NHS
South Yorkshire
Integrated Care Board

Tirzepatide (Mounjaro®) Kwikpen in adults 18 years and over with type 2 diabetes mellitus. (Note tirzepatide is also licensed for weight management, but this is not covered by this guideline).

Tirzepatide is Amber G in the South Yorkshire traffic light list for the treatment of insufficiently controlled Type 2 diabetes in adults.

The details of side-effects, cautions, contraindications and interactions are not a complete list and the current BNF https://bnf.nice.org.uk/drugs/tirzepatide/and the SPC (https://www.medicines.org.uk/emc/) remain authoritative.

The SY ICB Medicines Optimisation Team will alert primary care prescribers if any significant changes in review or monitoring arrangements of Amber-G medicines they prescribe are recommended.

Background Information	Tirzepatide is a combined GLP-1 (Glucagon-like-peptide-1) agonist and GIP (Glucose-dependant insulinotropic polypeptide agonist). Tirzepatide should be initiated by a specialist who has undertaken formal training or equivalent in the specialist area including e.g. Secondary care prescriber, GPSI, Diabetes specialist nurse and specialist pharmacists or practice nurses who have undertaken specialist training. Once the response to treatment has been established and side effects tolerated, ongoing prescribing can transfer to primary care/non specialist care with a clear care plan to consider dose titration or stopping if changes in response are not seen (see monitoring section below).

Indication	Tirzepatide is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise:
	• In addition to other medicinal products for the treatment of diabetes.
	• As monotherapy when metformin is considered inappropriate due to intolerance or contraindications. (Whilst tirzepatide is licensed for monotherapy, SY ICB promote the use of tirzepatide as outlined in the NICE TA 924 criteria).
	
	NICE TA 924 Clinical Guideline adults advises tirzepatide may be used if:
	• triple therapy with metformin and two other oral antidiabetic drugs is ineffective, not tolerated or contraindicated,(consider triple therapy by switching one drug for a GLP-1 agonist or tirzepatide) **and**
	• Patients must have a BMI of 35kg/m^2 or more, and specific psychological or other medical problems associated with obesity, **or**
	• Have a BMI less than 35kg/m^2, **and:**
	  ○ **For whom** insulin therapy would have significant occupational implications **or**
	  ○ weight loss would benefit other significant obesity-related complications.
	
	Use lower BMI thresholds (usually reduced by 2.5kg/m^2) for people from South Asia, Chinese, other Asian, middle Eastern, Black African or African-Caribbean family backgrounds.
	
	Patients currently prescribed a DPP4 inhibitor should have their medication reviewed and the DPP4 stopped prior to commencing a GLP-1 inhibitor.or tirzepatide. DPP4 inhibitors and GLP-1 agonists /tirzepatide should not be used in combination.

Dosage and administration	Tirzepatide solution for injection is provided as a prefilled oral solution Kwikpen (2.4ml) containing four doses of 0.6ml solution per dose (sufficient for 28 days supply).

	Tirzepatide solution for injection (Mounjaro®) is to be injected subcutaneously in the abdomen, thigh or upper arm. The dose can be administered at any time of day, with or without meals. Injection sites should be rotated with each dose. If a patient also injects insulin, they should inject Tirzepatide solution for injection (Mounjaro®) into a different injection site. Patients/carers should be counselled on injection technique and administration sites for injection (thigh, abdomen or upper arm). Patients should be advised to carefully read the instructions for use and the package leaflet for the pre-filled KwikPen before administering the medicinal product. The starting dose of tirzepatide is 2.5mg once weekly for 4 weeks**.** The specialist initiating tirzepatide should prescribe for the first 4 weeks (minimum) and review the patient before increasing the dose to 5mg. The patient should be maintained on a dose of **5mg** until the patient is reviewed **and** the **patient's** weight and HbA1c checked (3-6 months after tirzepatide initiation). Patients should be on a dose for a minimum of 4 weeks before any dose increase is considered. The usual maintenance doses are 5mg. 10mg or 15mg, with 15mg weekly being the maximum dose. If at the 6-month review, the patient is not meeting the following treatment targets: ○ Reduction in HbA1c of at least 11mmol/mol AND ○ Weight loss of at least 3% of initial body weight in 6 months. A review of tirzepatide prescribing should be conducted and *tirzepatide prescribing stopped if clinically appropriate (*This is not covered in NICE TA924 for tirzepatide but is recommended for GLP-1 agonists. To reduce the risk of treatment inertia NICE guidance should be followed). NICE TA924 states that in clinical trials the reduction of HbA1c was a flatter response curve and that increasing the dose did not significantly reduce the HbA1c. Higher doses do however, produce a statistically significant increase in weight loss. For those patients requiring further weight loss, an increase in dose may be considered. It is advised that the dose be increased to 7.5mg for 4 weeks, then 10mg until the next HbA1c/weight loss review. *Missed dose.* If a dose is missed, it should be administered as soon as possible within 4 days after the missed dose. If more than 4 days have passed, skip the missed dose and administer the next dose on the regular scheduled day. In each case, the patient should resume their regular once weekly dosing schedule (e.g. Patient usually administers on Saturday but goes away for the weekend and forgets to take the medication with them, they may administer on Sunday, Monday or Tuesday on their return. Should they return later than this then they should administer their next dose on Saturday and skip the missed dose). *Changing the dose schedule* The day of weekly administration can be changed, if necessary, as long as the time between two doses is at least 3 days. *Adding tirzepatide to existing metformin and/or SGLT2 inhibitor therapy* Current dose of metformin and/or SGLT2 inhibitor may be continued *Adding tirzepatide to existing sulphonylurea and/or insulin therapy* Patients taking a sulphonylurea or insulin in combination with tirzepatide are at an increased risk of hypoglycaemia. A reduction in the dose of sulphonylurea or insulin may be considered to reduce the risk of hypoglycaemia. Blood glucose self-monitoring is necessary to adjust the dose of sulphonylurea and insulin. A stepwise approach to insulin reduction is recommended. As the responses will be variable it is suggested that patients on these medications be given guidance by specialists with the knowledge to safely titrate sulphonylureas / insulin.

	Adding tirzepatide to gliptin therapy Adding tirzepatide therapy to gliptin therapy is not recommended as it has not been studied by the manufacturer. Tirzepatide and gliptins use similar pathways in the body by affecting incretin. It is thought that using them together may increase side effects such as acute pancreatitis
Precautions for use	When adding tirzepatide to existing metformin and/or sodium-glucose co-transporter 2 inhibitor (SGLT2i) therapy see the information contained in the dosage section above. When tirzepatide is added to existing therapy of a sulphonylurea and/or insulin therapy see the information contained in the dosage section above. No dose adjustment is needed based on age, gender, race, ethnicity or body weight. Patients of child bearing potential taking the oral contraceptive pill are advised to use an additional or alternate form of contraception on initiation of tirzepatide and at any tirzepatide dose increase (for a minimum of 4 weeks). This is in case vomiting or malabsorption occurs. Patients should be provided with suitable needles from the formulary and a Sharpsguard yellow sharps bin 5L for safe disposal of used needles. The yellow sharps bins should be disposed of through agreed place-based arrangements.
Cautions and Contraindications	**This list is not exhaustive, see BNF and SPC for full details.** **Contraindications** • Hypersensitivity to the active substances or any of the excipients. Cases of anaphylactic reaction and angioedema have been rarely reported with tirzepatide during post-marketing surveillance. **Cautions** *Acute pancreatitis* Tirzepatide has not been studied in patients with a history of pancreatitis. Avoid using in patients with a history of pancreatitis unless there is clear evidence that the precipitating cause is no longer cause for concern, in which it could be used with caution if benefits are thought to outweigh risks. Acute pancreatitis has been reported in patients treated with tirzepatide. Patients should be informed of the symptoms of acute pancreatitis. If pancreatitis is suspected, tirzepatide should be discontinued. If the diagnosis of pancreatitis is confirmed, tirzepatide should not be restarted. In the absence of other signs and symptoms of acute pancreatitis, elevations in pancreatic enzymes alone are not predictive of acute pancreatitis (see section 4.8 of the SPC). *Hypoglycaemia in patients with type 2 diabetes mellitus* Patients receiving tirzepatide in combination with an insulin secretagogue (for example, a sulphonylurea) or insulin may have an increased risk of hypoglycaemia. The risk of hypoglycaemia may be lowered by a reduction in the dose of the insulin secretagogue or insulin (see sections 4.2 and 4.8 of the SPC). Clinically significant hypoglycaemia (blood glucose < 3.0 mmol/L (< 54 mg/dL) or severe hypoglycaemia (requiring the assistance of another person) occurred in 10 to 14 % (0.14 to 0.16 events/patient year) of patients when tirzepatide was added to sulphonylurea and in 14 to 19 % (0.43 to 0.64 events/patient year) of patients when tirzepatide was added to basal insulin. *Gastrointestinal effects* Tirzepatide has been associated with gastrointestinal adverse reactions, which include nausea, vomiting, and diarrhoea (see section 4.8 of the SPC). These adverse reactions may lead to dehydration, which could lead to a deterioration in renal function including acute renal failure. Patients treated with tirzepatide should be advised of the potential

	risk of dehydration, due to the gastrointestinal adverse reactions and take precautions to avoid fluid depletion and electrolyte disturbances. This should particularly be considered in the elderly, who may be more susceptible to such complications. *Severe gastrointestinal disease* Tirzepatide has not been studied in patients with severe gastrointestinal disease, including severe gastroparesis, and should be used with caution in these patients. *Diabetic retinopathy* Tirzepatide has not been studied in patients with non-proliferative diabetic retinopathy requiring acute therapy, proliferative diabetic retinopathy or diabetic macular oedema, and should be used with caution in these patients with appropriate monitoring. *Elderly* Only very limited data are available from patients aged ≥ 85 years. *Sodium content* This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'. *Benzyl Alcohol [E1519]* This medicine contains 5.4 mg Benzyl Alcohol [E1519] in each 0.6 ml dose. Benzyl alcohol may cause allergic reactions. Patients with hepatic or renal impairment should be informed of the potential risk of metabolic acidosis due to accumulation of benzyl alcohol over time. Mounjaro® safety summary[9] from USA. The MHRA have not classified this warning in the SPC or BNF for the UK. This summary is for information only.[9] Mounjaro® may cause tumors in the thyroid, including thyroid cancer. Watch for possible symptoms, such as a lump or swelling in the neck, hoarseness, trouble swallowing, or shortness of breath. Advice patients if they have any of the above symptoms, tell the health care provider (GP, Nurse, Pharmacist etc).
Renal and Hepatic impairment	*Renal impairment* No dose adjustment is required for patients with renal impairment including end stage renal disease (ESRD). Experience with the use of tirzepatide in patients with severe renal impairment and ESRD is limited. Caution should be exercised when treating these patients with tirzepatide. *Hepatic impairment* No dose adjustment is required for patients with hepatic impairment. Experience with the use of tirzepatide in patients with severe hepatic impairment is limited. Caution should be exercised when treating these patients with tirzepatide.
Pregnancy and breast feeding	*Pregnancy* There are no or a limited amount of data from the use of tirzepatide in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Tirzepatide is not recommended during pregnancy and in women of childbearing potential not using contraception. If a patient wishes to become pregnant, tirzepatide should be discontinued at least 1 month (but preferably at least 3 months) before a planned pregnancy due to the long half-life of tirzepatide. Tirzepatide should not be used during pregnancy Alternative methods of controlling blood glucose levels should be discussed and initiated. *Breast feeding*

	It is unknown whether tirzepatide is excreted in human milk. A risk to the newborn/infant cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from tirzepatide therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. *Fertility* The effect of tirzepatide on fertility in humans is unknown.
Adverse Drug Reactions	**This list is not exhaustive, see BNF and SPC for full details.** *Very Common* • Hypoglycaemia when used with sulphonylureas or insulin • Nausea, diarrhoea, vomiting, constipation *Common* • Hypersensitivity reactions and injection site reactions • Hypoglycaemia when used with metformin and SGLT2 • Decreased appetite • Abdominal pian, dyspepsia, flatulence, GORD • Hair loss • Fatigue **Report side effect to the MHRA via the yellow card reporting site. Available at:** https://yellowcard.mhra.gov.uk/ The 7 completed phase 3 trial using tirzepatide alone or in combination with other glucose lowering medication showed that the most frequently reported adverse reactions were gastrointestinal disorders (nausea, constipation, diarrhoea and vomiting). In general, these reactions were mostly mild or moderate in severity and occurred more often during dose escalation and decreased over time.
Monitoring	Tirzepatide should be initiated by a specialist who has undertaken formal training or equivalent in the specialist area including e.g. Secondary care prescriber, GPSI, Diabetes specialist nurse and specialist pharmacists or practice nurses who have undertaken specialist training. Baseline monitoring (initiating specialist/clinician) • Weight • HbA1c (in appropriate patients) Initial monitoring (initiating specialist/clinician) • Review treatment after 4 weeks. Ensure the patient is rotating injection site, injecting correctly and any side effects are tolerable prior to increasing the dose to 5mg. This review should be undertaken by the initiating specialist/clinician. Primary care monitoring • Review patient and check HbA1c and weight every 3-6 months. See dosage section above for further information/consideration of dose titration.. • Dose escalation may be considered after discussion with initiating specialist. If a dose increase is appropriate the patient should be reviewed every 4 weeks whilst the dose is increasing. • If the patient is not meeting the reduction in HbA1c of at least 11mmol/mol AND Weight loss of at least 3% of initial body weight at each of the 6 monthly reviews, then stopping tirzepatide may be considered. This may be discussed with a specialist from the list above (either primary or secondary care) prior to stopping.
Interactions	**This list is not exhaustive, see BNF and SPC for full details.**

	Tirzepatide delays gastric emptying. MHRA drug safety alert January 2025 advises that delaying gastric emptying may increase the risk of residual gastric contents despite pre-operative fasting, leading to the potential risk of pulmonary aspiration. Delayed gastric emptying also has the potential to impact the rate of absorption of concomitantly administered oral medicinal products. This effect, resulting in decreased Cmax and a delayed Tmax, is most pronounced at the time of tirzepatide treatment initiation. <u>Drugs with a narrow therapeutic index</u> Monitor all patients on oral medicinal products with a narrow therapeutic index (e.g. warfarin, digoxin) especially on initiation of tirzepatide treatment. <u>Paracetamol</u> No dosage adjustment necessary. Following a 5mg single dose of tirzepatide the max plasma concentration of paracetamol was reduced by 50% and median was delayed by 1 hour. <u>Oral contraceptives</u> No dose adjustments required in patients with a normal BMI. In overweight or obese women, it is advisable to switch to a non-oral contraceptive method, or add a barrier method of contraception upon initiating tirzepatide therapy (for 4 weeks), or after each dose increase (for 4 weeks). As one of the most common side effects on initiation with tirzepatide is vomiting it is advisable to advise patients to switch to a non-oral method or add a barrier method of contraception.
Patient information	Patients should be counselled by the initiating prescriber on: • Priming of the device: Each Kwikpen contains 4 doses. To prime the device, slowly turn the nob until two clicks are heard. Hold the pen with the needle pointing up and tap cartridge gently to collect air bubbles at the top. Release some medicine by pushing the dose knob until it stops. Count to 5 whilst holding the knob. The dose window should now read zero. • Injecting: Dial the dose by turning the knob until it stops at '1'. This is equivalent to a dose of 0.6ml. • Correct injection technique • Injection site use and rotation of injection site • Tirzepatide (Mounjaro®) may be removed from fridge 30min prior to injecting to help reduce stinging at injection site on administration of injection. • Drinking enough water (Minimum 6-8 glasses per day). Please provide patient with a patient information leaflet. Available at: https://www.medicines.org.uk/emc/product/15481/pil. The patient may also wish to follow the 'How to use Mounjaro® Kwikpen® step by step instructions online. Available at:https://medical.lilly.com/uk/products/answers/how-to-use-the-mounjaro-tirzepatide-kwikpen-219072

Contact names and details

Contact Details	**Email**
Sheffield	jackie.elliott6@nhs.net Or contact the local diabetes specialist nurses or community specialist diabetes nurses
Rotherham	diabetes.specialistnursing@nhs.net
Doncaster	Secondary care secretaries dbth.diabsec@nhs.net Primary care diabetes specialist nurse team RDASH.DiabetesYASReferrals@nhs.net

Barnsley	Secondary care secretaries: bdgtr.endodiab.secretaries@nhs.net Primary care diabetes specialist nurse team: barnsleydiabetes.spa@nhs.net

This guidance has been reviewed by Dr Jackie Elliott clinical lead for diabetes Sheffield Teaching Hospital.

Equality and diversity

NICE TA 924 advises using lower BMI thresholds (usually reduced by 2.5kg/m^2) for people from South Asia, Chinese, other Asian, middle Eastern, Black African or African-Caribbean family backgrounds. Further information regarding BMI can be accessed via the indication section of the document.

References

1. Summary of Product Characteristics:Tirzepatide (Mounjaro®) 2.5mg solution for injection. Available at:https://www.medicines.org.uk/emc/product/15481/smpc <Accessed 17/07/2024>
2. Summary of Product Characteristics:Tirzepatide (Mounjaro®) 5mg solution for injection. Available at: https://www.medicines.org.uk/emc/product/15482/smpc. <Accessed 17/07/2024>
3. Summary of Product Characteristics:Tirzepatide (Mounjaro®) 7.5mg solution for injection. Available at: https://www.medicines.org.uk/emc/product/15483. <Accessed 17/07/2024>
4. Summary of Product Characteristics:Tirzepatide (Mounjaro®) 10mg solution for injection. Available at: https://www.medicines.org.uk/emc/product/15484. <Accessed 17/07/2024>
5. Summary of Product Characteristics:Tirzepatide (Mounjaro®) 12.5mg solution for injection. Available at: https://www.medicines.org.uk/emc/product/15485 <Accessed 17/07/2024> (Note not currently available in the UK July 2024)
6. Summary of Product Characteristics:Tirzepatide (Mounjaro®) 15mg solution for injection. Available at: https://www.medicines.org.uk/emc/product/15486. <Accessed 17/07/2024>(Note not currently available in the UK July 2024)
7. NICE Clinical Guideline. Available at:https://www.nice.org.uk/guidance/ta924/chapter/3-Committee-discussion <Accessed 17/07/2024>
8. Responsibility for prescribing between Primary and Secondary care. Available at:https://www.england.nhs.uk/wp-content/uploads/2018/03/responsibility-prescribing-between-primary-secondary-care-v2.pdf.<Accessed 17/07/2024>
9. Mounjaro® safety summary from the USA for information only.. Available at : https://mounjaro.lilly.com/once-weekly-mounjaro.<Accessed 01/10/2024>.
10. NICE guidance NG 28. Avalable at: https://www.nice.org.uk/guidance/ng28/chapter/Recommendations. <Accessed Jan 2025>.