# Tirzepatide for Type 2 Diabetes in Adults

## Prescribing Support Document

### What is it?

Tirzepatide is a long-acting dual glucose-dependent insulinotropic polypeptide (GIP) receptor agonist and glucagon-like peptide-1 (GLP-1) receptor agonist. It works by mimicking the GIP and GLP-1 hormones to increase insulin sensitivity and secretion, suppress glucagon secretion and slow gastric emptying. It is an approved drug for the management of type 2 diabetes mellitus (T2DM).

The multinational multicentre randomised phase 3 studies conducted in the SURPASS trials have shown tirzepatide provides significant improvements in glycaemic control, with clinically meaningful HbA1c reduction and a low incidence of hypoglycaemia is associated with tirzepatide.

### NICE Guidance

NICE Technology Appraisal Guidance (TA924; published 25th October 2023) states:

Tirzepatide is recommended for treating type 2 diabetes alongside diet and exercise in adults when it is insufficiently controlled only if:

- triple therapy with metformin and two other oral antidiabetic drugs is ineffective, not tolerated or contraindicated, **and**
- they have a body mass index (BMI) of 35 kg/m$^2$ or more, and specific psychological or other medical problems associated with obesity, **or**
- they have a BMI of less than 35 kg/m$^2$, **and**:
    - insulin therapy would have significant occupational implications, **or**
    - weight loss would benefit other significant obesity-related complications.

Use lower BMI thresholds (usually reduced by 2.5 kg/m$^2$) for people from South Asian, Chinese, other Asian, Middle Eastern, Black African or African-Caribbean family backgrounds.

This recommendation is not intended to affect treatment with tirzepatide that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Please refer to the Cambridgeshire and Peterborough system-wide formulary for links to local and national guidance.

Where a GLP-1 like mimetic is clinically indicated and the patient fulfils the NICE criteria above, tirzepatide should be used:

- Second line (GLP-1 like mimetic) where a trial of semaglutide (subcutaneous) (first line GLP-1 mimetic) has not been effective after six months.
- Tirzepatide may be considered as first line GLP-1 like mimetic for the following patient cohorts in whom semaglutide would not be able to achieve remission:
    - patients in whom HbA1c is 64 mmol/mol or more
    - patients with multiple obesity-related co-morbidities
    - patients already referred for tier 3 obesity services
    - patients in whom bariatric surgery is being considered

## Licensed indications and prescribing good practice

### Which health professionals will prescribe?

Tirzepatide can be prescribed by both primary care and secondary care clinicians for patients with type 2 diabetes mellitus who meet the criteria set out in NICE TA924. Secondary care clinicians may identify eligible patients through diabetes clinics or hospital admission, but primary care clinicians can also initiate tirzepatide therapy in the community.

If patient is already prescribed insulin therapy, tirzepatide must be recommended by a specialist with relevant expertise, including diabetes specialist nurse.

## Preparations and Dosage

### Preparation

Tirzepatide (Mounjaro KwikPen):

- 2.5mg/0.5mL solution for injection pre-filled pen.
- 5mg/0.5mL solution for injection pre-filled pen.
- 7.5mg/0.5mL solution for injection pre-filled pen.
- 10mg/0.5mL solution for injection pre-filled pen.
- 12.5mg/0.5mL solution for injection pre-filled pen.
- 15mg/0.5mL solution for injection pre-filled pen.

Each multiple dose pre-filled pen contains 4 doses.

### Dosage and Administration

Administered by subcutaneous injection in the abdomen, thigh or upper arm. The dose can be administered at any time of day, with or without meals.

Initially 2.5mg once weekly for 4 weeks, then increased to 5 mg once weekly for at least 4 weeks. If needed, dose increases can be made in 2.5mg increments at intervals of at least 4 weeks, up to a maximum dose of 15 mg once weekly. The recommended maintenance doses are 5 mg, 10 mg or 15 mg once weekly.

When tirzepatide is added to existing metformin and/or sodium-glucose co-transporter 2 inhibitor (SGLT2i) therapy, the current dose of metformin and/or SGLT2i can be continued.

When tirzepatide is added to existing therapy of a sulfonylurea and/or insulin, a reduction in the dose of sulfonylurea or insulin may be considered to reduce the risk of hypoglycaemia. A stepwise approach to insulin reduction is recommended to reduce the risk of diabetic ketoacidosis associated with rapid reduction or discontinuation of concomitant insulin (MHRA guidance June 2019). Self-blood glucose monitoring or use of a continuous glucose monitor (CGM) is necessary to adjust the sulfonylurea and/or insulin dose.

## Contraindications and cautions

### Contraindications

- Hypersensitivity to tirzepatide or excipients (including benzyl alcohol).
- Personal or family history of medullary thyroid cancer or multiple endocrine neoplasia 2A or 2B.

### Cautions

- History of pancreatitis
- Severe gastrointestinal disease, including severe gastroparesis.
- Non-proliferative diabetic retinopathy requiring acute therapy, proliferative diabetic retinopathy and diabetic macular oedema.

No dose adjustment is needed based on age, gender, race, ethnicity or body weight.

The safety and efficacy of tirzepatide in children aged less than 18 years have not yet been established and only very limited data are available from patients aged ≥ 85 years.

No dose adjustment is required for patients with hepatic impairment or renal impairment including end stage renal disease (ESRD), but experience with the use of tirzepatide in these patients is limited and caution should be exercised when treating these patients with tirzepatide. Patients with hepatic or renal impairment should be informed of the potential risk of metabolic acidosis due to accumulation of benzyl alcohol over time.

## Drug interactions

Below are some general drug interactions but prescribers must consult the Summary of Product Characteristics for more detailed information on each specific drug. This is not an exhaustive list.

| **Drug/ Therapeutic group** | **Interaction** |
|---|---|
| Antidiabetic medications | Concomitant use of tirzepatide and insulin or sulfonylureas can lead to an increased risk of hypoglycaemia. A lower dose of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycaemia in patients with T2DM. A low risk of hypoglycaemia also exists when tirzepatide is concomitantly administered with other antidiabetic agents. |
| Medicines with a narrow therapeutic index (e.g. warfarin, digoxin) | Tirzepatide delays gastric emptying and can impact the rate of absorption of other oral medications. This is most pronounced at the time of tirzepatide initiation. Monitor patients on medicines with a narrow therapeutic index (e.g. warfarin, digoxin), especially at initiation of tirzepatide treatment and following dose increase. |

| Drug/ Therapeutic group | Interaction |
|---|---|
| Oral contraceptives | There is limited information about the effect of tirzepatide on the efficacy of oral contraceptives in female patients who are overweight or obese. Since reduced efficacy of oral contraceptives cannot be excluded, it is advised switching to a non-oral contraceptive method, or add a barrier method of contraception for the first 4 weeks after initiating tirzepatide therapy, and for 4 weeks after **each** dose escalation. |

## Adverse effects

| Type | Adverse effect |
|---|---|
| Common side effects (gastrointestinal) | The most frequently reported adverse reactions are gastrointestinal disorders including abdominal pain and distension, dyspepsia, flatulence, constipation, diarrhoea, nausea and vomiting – potential risk of dehydration. Initiating at a low dose and increasing the dose slowly can help to avoid adverse gastrointestinal side effects. |
| Other side effects | **Acute pancreatitis** (uncommon)<br>Inform patients 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.<br><br>**Hypoglycaemia**<br>Very common when tirzepatide used with sulfonylurea and/or insulin<br>• Patients receiving tirzepatide in combination with a sulfonylurea and/or insulin may have an increased risk of hypoglycaemia. A reduction in the dose of sulfonylurea or insulin may be considered to reduce the risk of hypoglycaemia. A stepwise approach to insulin reduction is recommended to reduce the risk of diabetic ketoacidosis associated with rapid reduction or discontinuation of concomitant insulin (MHRA guidance June 2019). Self-blood glucose monitoring is necessary to adjust the sulfonylurea and/or insulin dose.<br><br>Common when tirzepatide used with metformin or SGLT2i,<br>Uncommon when tirzepatide used with metformin monotherapy<br>• No dose adjustment required for other antidiabetic medications when used concomitantly with tirzepatide.<br><br>**Other side effects**<br>Common: hypersensitivity, decreased appetite, dizziness, hypotension, asthenia, lethargy, malaise, increased heart rate, increased pancreatic enzymes (lipase, amylase)<br>Uncommon: cholelithiasis, cholecystitis<br>Rare: anaphylactic reaction, angioedema |

Frequency categories: 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), very rare (< 1/10,000).

**For full details on cautions, contraindications, drug interactions and adverse effects, please consult the latest edition of the British National Formulary (BNF) or Summary of Product Characteristics (SPC).**

## Pregnancy and breastfeeding

### 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. 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 before a planned pregnancy due to the long half-life of tirzepatide. Tirzepatide should not be used during pregnancy.

### Breastfeeding

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 breastfeeding or to discontinue/abstain from tirzepatide therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

### Fertility

The effect of tirzepatide on fertility in humans is unknown. Animal studies with tirzepatide did not indicate direct harmful effects with respect to fertility.

## Monitoring: Specialist responsibility

No responsibility for routine monitoring.

## Monitoring: Primary care responsibility

A baseline retinal examination must be performed within the 12 months before tirzepatide initiation. Review patients every 6 months for clinical effectiveness within the first year, and then every 12 months thereafter. **Only continue GLP-1 mimetic therapy if the adult with type 2 diabetes has had a beneficial metabolic response (a reduction of at least 11 mmol/mol [1.0%] in HbA1c and weight loss of at least 3% of initial body weight in 6 months.** Routine monitoring appropriate for T2DM should continue.

- ▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme.

## Missed doses

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 regularly scheduled day. In both cases, patients can resume their regular once weekly dosing schedule. The time between two doses of tirzepatide must be at least 3 days.

## Stopping therapy

Stop tirzepatide if:

- Acute pancreatitis develops.
- Patients have not achieved a beneficial metabolic response (a reduction of at least 11 mmol/mol (1%) in HbA1c and weight loss of at least 3% of initial body weight in 6 months).

## Advice and Support

| **Issue** | **Management** |
|---|---|
| Glycaemic control | A lower dose of insulin or sulfonylurea may be required to reduce the risk of hypoglycaemia when used in combination with tirzepatide in patients with T2DM.<br>Rapid or large reductions of insulin dose may precipitate diabetic ketoacidosis and should be avoided.<br>No dose adjustment required for other antidiabetic medications when used concomitantly with tirzepatide. |
| Diabetic ketoacidosis | "Sick day" rules. Advise patients to maintain fluid and carbohydrate intake (do not fast). Increased risk if patient experiences gastrointestinal side effects leading to dehydration or rapid or large reductions of concomitant insulin dose.<br>Seek urgent medical advice if unable to keep fluids/food down. |
| Acute pancreatitis | Patients and their carers should be told how to recognise signs and symptoms of acute pancreatitis and advised to seek immediate medical attention if symptoms develop. If acute pancreatitis diagnosed, stop tirzepatide immediately and do not restart. |
| Dehydration | Patients and their carers should be informed of the potential risk of dehydration in relation to gastrointestinal side effects and advised to take precautions to avoid fluid depletion. |

Contact local diabetes specialist team if further support is required, particularly if tirzepatide is stopped due to adverse effects.

## References


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## Document ratification details

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