Mounjaro in Alstrom Syndrome

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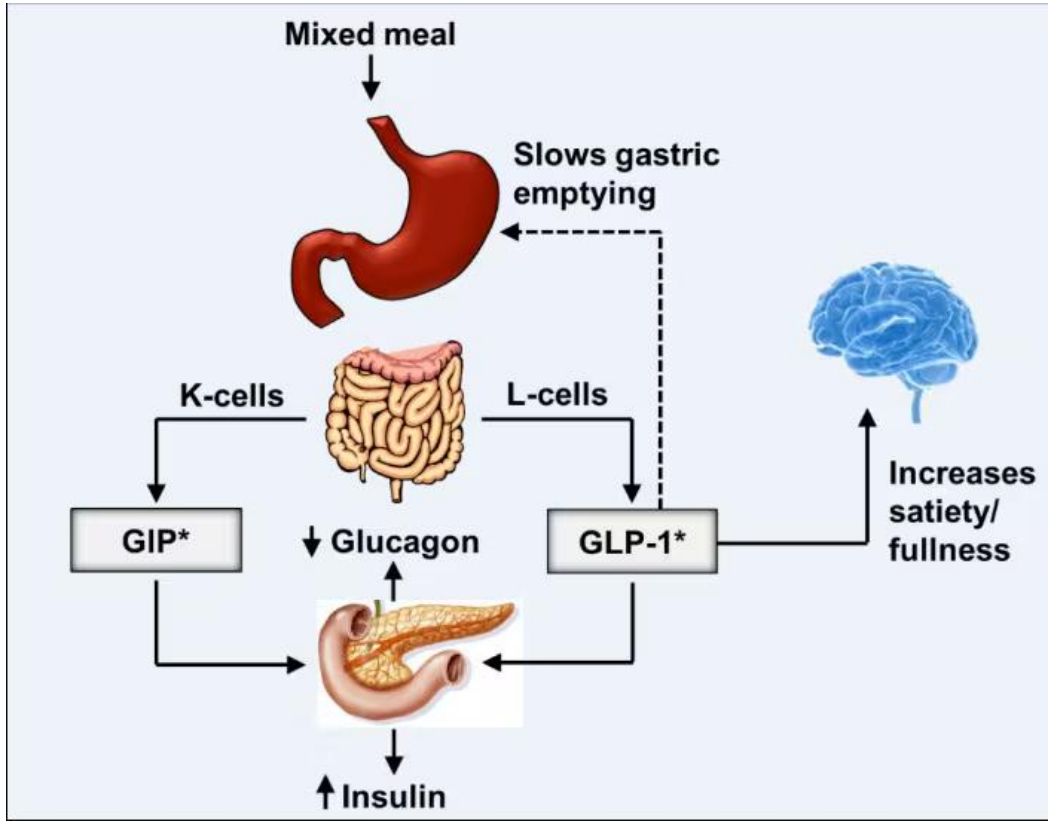
OVERVIEW

- Introduction, how does it work, dosing
- Evidence base around efficacy
- Safety profile
- Contraindications & Cautions
- UK regulations NHS England eligibility & Pathway
- FAQ’s

What is tirzepatide (Mounjaro)?



- A once-weekly dual GIP and GLP-1 receptor agonist indicated in the UK for weight management and for type 2 diabetes.
- Licensed name in the UK: Mounjaro. US obesity brand: Zepbound.
- Mechanism: enhances glucose-dependent insulin secretion; slows gastric emptying; promotes satiety and reduced energy intake.
- GLP-1 agonists help regulate blood sugar post-meal by stimulating insulin secretion, suppressing glucagon secretion, and slowing gastric emptying.
- GIP agonists complement this by not only boosting insulin secretion but also enhancing the body's insulin sensitivity.
- This approach addresses the underlying symptom of insulin resistance in type 2 diabetes, setting Mounjaro apart from other treatments like Semaglutide and liraglutide, which lack the additional benefit of GIP activation.

↑ insulin secretion secretion (glucose dependent), satiety

↓ Glucagon, , slows gastric emptying

- Reduced glucose dependent insulin secretion after meals
- Inadequate suppression of glucagon
- Post prandial hyperglycaemia
- Less satiety signalling

How does Mounjaro support weight loss?

- **Reducing appetite**
- Mounjaro delays gastric emptying which promotes a sense of fullness, reduces appetite and naturally reduces calorie intake, and helps to regulate blood sugar levels by slowing down the absorption of glucose from food.
- **Increasing energy expenditure**
- Mounjaro activates receptors that boost metabolic rate and energy use, aiding in calorie burning.
- **Improving insulin sensitivity**
- The modulation of GIP receptors enhances glucose utilisation, contributing to sustained satiety and weight maintenance.

Dosing and titration (BNF / UK device)

Start 2.5 mg once weekly for 4 weeks, then increase by 2.5 mg every 4 weeks to 5 mg, 7.5 mg, 10 mg, 12.5 mg and 15 mg as tolerated.

Missed dose: if >4 days late, omit and take next dose at the usual time (per UK local guidance/BNF).

Each KwikPen contains 4 doses (monthly pack). Four-dose KwikPen approved by MHRA in Jan 2024.

Patient counselling points

- Administration: once-weekly SC injection; rotate sites (abdomen, thigh, upper arm).
- Titration pace is to improve tolerability; do not up-titrate faster than every 4 weeks.
- If severe or persistent GI symptoms occur, pause escalation or step back a dose.
- Maintain reduced-calorie diet and increased physical activity; set realistic goals.

Efficacy: SURMOUNT-1 (NEJM 2022; adults without diabetes; 72 weeks)

- Mean % weight change at week 72 (treatment-regimen estimand):
- • 5 mg: −15.0% (95% CI −15.9 to −14.2)
- • 10 mg: −19.5% (95% CI −20.4 to −18.5)
- • 15 mg: −20.9% (95% CI −21.8 to −19.9)
- • Placebo: −3.1% (95% CI −4.3 to −1.9)
- Response thresholds at week 72:
  - ≥5% weight loss: 85% (5 mg), 89% (10 mg), 91% (15 mg) vs 35% placebo
  - ≥20% weight loss: 50% (10 mg), 57% (15 mg) vs 3% placebo

Efficacy: SURMOUNT-2 (Lancet 2023; Obesity with T2D; 72 weeks)

- Least-squares mean % weight change at week 72:
- • 10 mg: −12.8% (SE 0.6)
- • 15 mg: −14.7% (SE 0.5)
- • Placebo: −3.2% (SE 0.5)
- Estimated treatment differences vs placebo: −9.6 and −11.6 percentage points (both $p<0.0001$).
- ≥5% weight loss achieved in 79–83% on tirzepatide vs 32% with placebo.

Efficacy: SURMOUNT-3 (Nat Med 2023; post-lifestyle lead-in; 72 weeks)

- Participants first lost ≥5% with 12-week intensive lifestyle intervention, then randomised.
- Additional mean % weight change from randomisation to week 72: −18.4% (SE 0.7) with tirzepatide vs +2.5% (SE 1.0) with placebo.
- Percentage achieving additional ≥5% weight loss: 87.5% vs 16.5% (OR 34.6; 95% CI 19.2–62.6; p<0.001).

Efficacy: SURMOUNT-4 (JAMA 2024; maintenance vs withdrawal; 88 weeks)

- After 36 weeks open-label tirzepatide, participants were randomised to continue tirzepatide or switch to placebo.
- Withdrawing tirzepatide led to substantial weight regain; continued therapy maintained and further augmented weight loss.
- Conclusion: obesity requires ongoing treatment to sustain benefits.

Longer-term outcomes and diabetes prevention

- SURMOUNT-1 extension (2025): 3-year data in those with prediabetes showed sustained weight reduction and delayed progression to type 2 diabetes with tirzepatide versus placebo.

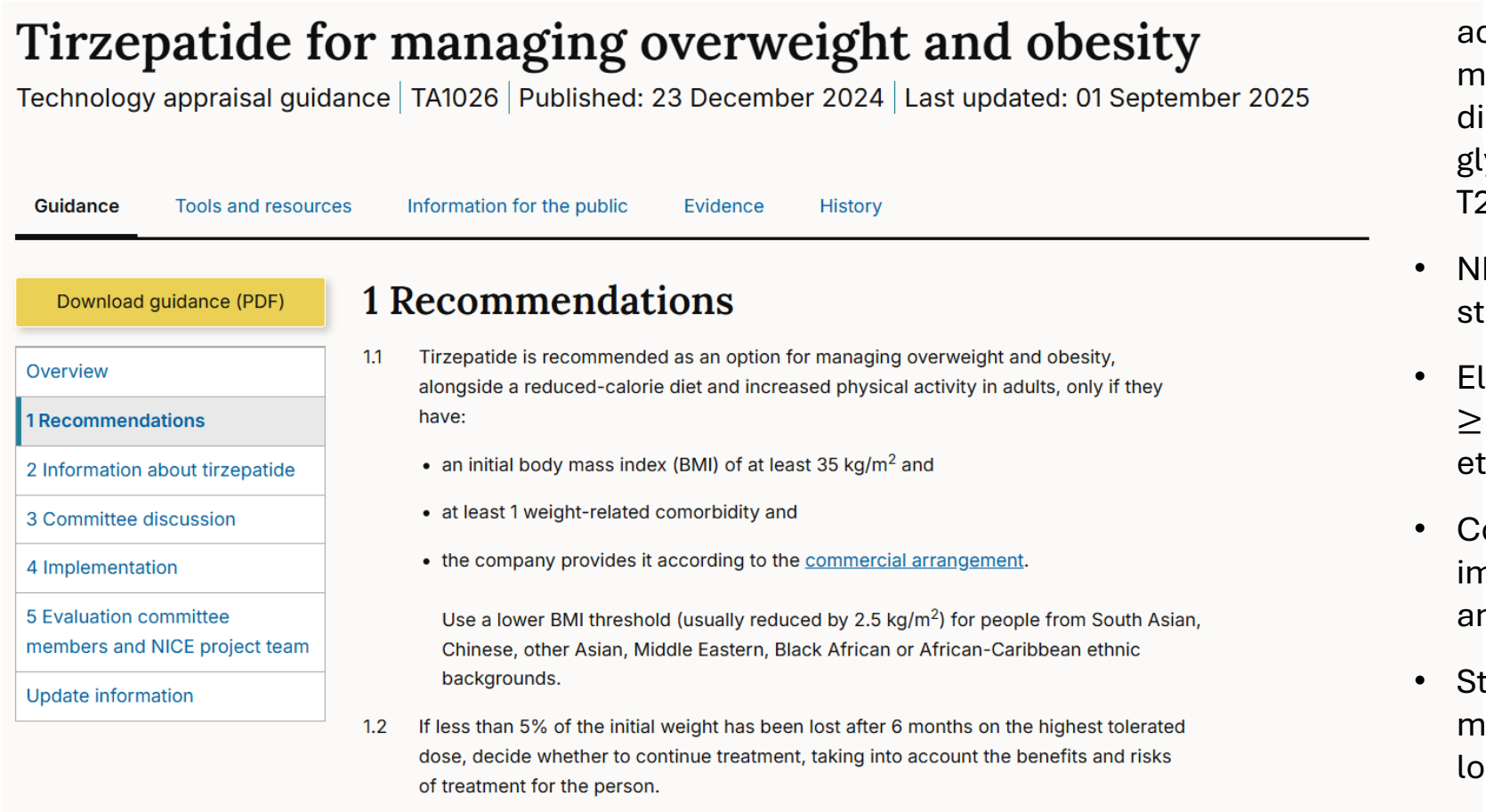
Safety profile (across trials and BNF)

- Common adverse effects (usually during dose escalation):
  - Nausea, diarrhoea, vomiting, constipation, abdominal pain; generally mild-to-moderate.
- Cholelithiasis/pancreatitis:
  - Caution; advise patients to report severe abdominal pain. Discontinue if pancreatitis suspected.
- GI motility:
  - Delays gastric emptying, especially after first dose. May affect absorption of oral medicines with narrow therapeutic index.
- Contraception:
  - May reduce absorption of combined oral contraceptives during dose escalation; advise additional contraception for 4 weeks after starting and after each dose increase (per BNF/manufacturer).
- Hypoglycaemia risk:
  - Low when used without insulin/sulphonylurea; risk increases if combined with these.
- Renal:
  - GI losses can precipitate dehydration and worsen renal function; monitor if at risk.

Contraindications and cautions (UK)

- Contraindicated in hypersensitivity to tirzepatide or excipients.
- Caution in history of pancreatitis, severe GI disease, gallbladder disease.
- Avoid in pregnancy and during breast-feeding; discontinue if planning pregnancy.
- Not a substitute for insulin in T1D or DKA; not indicated in under-18s for weight management (as of Sep 2025).

Practical NHS use (England) – eligibility & pathway



Tirzepatide for managing overweight and obesity

Technology appraisal guidance | TA1026 | Published: 23 December 2024 | Last updated: 01 September 2025

Guidance | Tools and resources | Information for the public | Evidence | History

Download guidance (PDF)

Overview
1 Recommendations
2 Information about tirzepatide
3 Committee discussion
4 Implementation
5 Evaluation committee members and NICE project team
Update information

1 Recommendations

1.1 Tirzepatide is recommended as an option for managing overweight and obesity, alongside a reduced-calorie diet and increased physical activity in adults, only if they have:

- an initial body mass index (BMI) of at least 35 kg/m^2 and
- at least 1 weight-related comorbidity and
- the company provides it according to the commercial arrangement.

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

1.2 If less than 5% of the initial weight has been lost after 6 months on the highest tolerated dose, decide whether to continue treatment, taking into account the benefits and risks of treatment for the person.

- On 13 May 2022, the Food and Drug Administration (FDA) approved Tirzepatide once-a-week subcutaneous injections (with the dose adjusted based on tolerability to achieve blood glucose targets) as monotherapy or combination therapy, with diet and physical exercise, to achieve better glycemic blood levels in patients affected by T2DM
- NICE TA1026 Dec 2024: prescribe alongside a structured weight-management programme.
- Eligibility includes initial BMI ≥35 kg/m^2 plus ≥1 comorbidity; lower thresholds for certain ethnic groups per NICE.
- Commissioning is phased; local ICB implementation may vary; verify local criteria and supply status.
- Stop rule: many services review at ~6 months; discontinue if <5% weight loss (per local policy).

Tirzepatide for treating type 2 diabetes

Technology appraisal guidance | TA924 | Published: 25 October 2023 | Last updated: 01 September 2025

Download guidance (PDF)

1 Recommendations

1.1 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 2 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.

Pathway for Medication Implementation After NICE Approval (Text Outline)

1. **NICE Approval Issued**
   ↓
2. **Publication of Technology Appraisal (TA) or Guidance**
   ↓
3. **Local NHS Organisations Review Guidance**
   - Integrated Care Boards (ICBs) / Trust Medicines Committees
     ↓
4. **Inclusion on Local Formularies**
   - Develop implementation plans
   - Update prescribing policies
     ↓
5. **Training & Communication to Clinicians**
   - Disseminate clinical guidance
   - Training sessions for prescribers and pharmacists
     ↓
6. **Funding & Commissioning Arrangements**
   - Funding mandated within 90 days of NICE guidance (statutory requirement in England)
     ↓
7. **Patient Identification & Eligibility Assessment**
   - Clinicians identify patients meeting criteria
     ↓
8. **Prescribing & Monitoring Initiated**
   - Medication supplied according to local pathways
   - Ongoing monitoring for safety and effectiveness
     ↓
9. **Audit & Feedback**
   - Data collection and review
   - Continuous quality improvement

FAQ’s

1) Why aren’t all patients with Alström Syndrome on Mounjaro?

- • Limited evidence specific to Alström Syndrome
- • Rare disease: no large-scale clinical trials
- • Access restricted by licensing and funding rules
- • Treatment must be individualised
- (PubMed: PMID 36863149, PMID 37174372)

2) Why some patients on Semaglutide and some on Mounjaro?

- • Semaglutide = GLP-1 agonist only
- • Mounjaro = dual GIP/GLP-1 agonist
- • Trials (SURPASS/SURMOUNT) show Mounjaro leads to greater weight loss
- • Choice depends on licensing, availability, and tolerance
- (PubMed: PMID 35658024, PMID 37275349)

3) Benefits for Alström patients

- • Potential improvement in obesity and metabolic control
- • May help reduce liver fat, insulin resistance, cardiovascular risk
- • No Alström-specific RCTs yet
- (PubMed: PMID 36863149)

4) Why some do not lose weight on Mounjaro?

- • Genetic variability in response
- • Compensatory appetite or lifestyle factors
- • Underlying hormonal/metabolic conditions
- • Adherence issues
- (PubMed: PMID 37275349)

What hormones does Mounjaro impact?

- • Mounjaro mimics GIP and GLP-1
- • Increases insulin secretion, decreases glucagon
- • Slows gastric emptying, reduces appetite
- • Impacts satiety centres in the brain
- (PubMed: PMID 35658024)

5) Impact on Obesity

- • Average 15–22% body weight loss in SURMOUNT trials
- • Improves HbA1c, lipid profile, liver fat
- • Reduces risk of obesity-related comorbidities
- (PubMed: PMID 35658024, PMID 37275349)

6) Side-effects and Management

- • Common: nausea, vomiting, diarrhoea, constipation
- • Usually dose-dependent and transient
- • Management: smaller meals, hydration, slower dose escalation
- • Rare: pancreatitis, gallbladder disease
- (PubMed: PMID 35658024)

7) Research & Future Directions

- • SURMOUNT and SURPASS trials: strong evidence in diabetes/obesity
- • Ongoing trials in non-diabetic obesity
- • No dedicated RCTs in Alström yet but case reports emerging
- • Further rare disease research anticipated
- (PubMed: PMID 37275349)

8) What if GP/hospital won’t prescribe?

- • Currently licensed only for diabetes in many regions
- • NICE guidance evolving for obesity
- • Patients may need referral to specialist weight management/endocrine teams
- • Clinical trial participation is another route
- (PubMed: PMID 36863149)

9) Alcohol and Mounjaro

- • No absolute contraindication
- • Alcohol can worsen GI side-effects and affect glucose control
- • Best to limit or avoid
- (PubMed: Clinical pharmacology guidance)

10) Foods and Drinks to Avoid

- • No strict prohibited foods
- • Fatty, spicy, large meals may worsen GI effects
- • Encourage balanced diet high in fibre, protein, low in refined sugar
- (PubMed: Nutrition and GLP-1 analogues literature)

- THANK YOU