Surrey Heartlands Integrated Care System
Area Prescribing Committee (APC)

Integrated Care Partnership - Surrey Downs, Guildford & Waverley, North-West Surrey, and East Surrey Places & associated partner organisations.

NICE Technology Appraisals (TA) briefing paper for local implementation.

NICE TA Guidance name and number	Tirzepatide for treating type 2 diabetes: TA 924		
Available at	Overview | Tirzepatide for treating type 2 diabetes | Guidance | NICE		
Date of issue	25 October 2023	**Implementation deadline**	3 months

Medicine details[1]	
Name and brand name	Generic name (Brand name) Tirzepatide (Mounjaro ®)
Manufacturer	Lilly
Mode of action	Tirzepatide is a long-acting dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist. Both receptors are present on the pancreatic α and β endocrine cells, brain, heart, vasculature, immune cells (leukocytes), gut and kidney. GIP receptors are also present on adipocytes. Tirzepatide is highly selective and has a high affinity to human GIP and GLP-1 receptors. The activity of tirzepatide on the GIP receptor is similar to native GIP hormone. The activity of tirzepatide on the GLP-1 receptor is lower compared to native GLP-1 hormone.
Licensed indication	Tirzepatide is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise. • as monotherapy when metformin is considered inappropriate due to intolerance or contraindications • in addition to other medicinal products for the treatment of diabetes.
Formulation	Tirzepatide ® solution for subcutaneous injection for all doses; 2.5mg,5mg,7.5mg,10mg, 12.5mg, 15mg – **device has yet to be confirmed by the manufacturer in relation to this TA. The company indicate that it is highly likely that the device will be a pre-filled pen. They are awaiting MHRA approval for the new device.**
Dosage	The starting dose of tirzepatide is 2.5 mg once weekly. After 4 weeks, the dose should be increased to 5 mg once weekly. If needed, dose increases can be made in 2.5 mg increments after a minimum of 4 weeks on the current dose.

	The recommended maintenance doses are 5, 10 and 15 mg. The maximum dose is 15 mg once weekly.
Comparison of NICE TA with Summary of Product Characteristics (SmPC)[2]	Some people with type 2 diabetes have triple therapy with metformin and 2 other oral antidiabetic drugs. When this is ineffective, not tolerated, or contraindicated, they may switch to a glucagon-like peptide-1 (GLP-1) receptor agonist (such as semaglutide) or start insulin therapy. For this evaluation, the company asked for tirzepatide to be considered only as an alternative to GLP-1 receptor agonists. However, to note, this does not encompass all individuals for whom tirzepatide is licensed.

NICE TA recommendations[2]

Recommendations

Tirzepatide is recommended for treating adults with 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/m2 or more, and specific psychological or other medical problems associated with obesity, **OR**
- they have a BMI of less than 35 kg/m2, **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/m2) for people from South Asian, Chinese, other Asian, Middle Eastern, Black African or African-Caribbean family backgrounds.

Decision making framework (DMF)

National guidance and priorities

The ICS has a legal obligation to commission this medicine in line with the NICE TA.

- This NICE TA has been assigned an implementation deadline of 3 months.
- The implementation deadline is 24th January 2023 but as the supply of tirzepatide was not available at that time, implementation has been delayed until March 2024.

Clinical effectiveness

Tirzepatide a dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist. Tirzepatide is the first medication in the GIP/GLP-1 receptor agonist drug class.

The clinical-effectiveness evidence for tirzepatide came only from 4 out of the 6 SURPASS trials: SURPASS 2,3,4 and 5. These were multinational multicentre randomised phase 3 studies designed to mimic the typical clinical progression of Type 2 Diabetes.

They assessed Tirzepatide 5 mg, 10 mg and 15 mg against:

1. placebo and no other medication

2. semaglutide in adults with T2DM who had inadequate control on metformin alone (1500mg or more/day)

3. insulin Degludec in adults with T2DM who had inadequate control on a stable dose of metformin +/- SGLT2i

4. insulin glargine in adults with T2DM with a high risk of cardiovascular disease and inadequate glycaemic control on stable doses of at least 1 and no more than 3 oral antiglycaemic agents – including metformin, SGLT2i and/or sulphonylurea

5. placebo in adults with T2DM and on Insulin glargine +/- metformin

6. insulin lispro in adults with T2DM

Clinical trial results suggest that tirzepatide shows greater benefit in reducing blood glucose levels (measured by HbA1c levels) and body weight compared with semaglutide, insulin therapy or placebo. There is only an indirect comparison of tirzepatide with other GLP-1 receptor agonists, which suggests similar benefits, although these results are less certain.

The committee concluded that tirzepatide (all doses) showed statistically significant reductions in HbA1c and body weight compared with all comparators in SURPASS trials. It also concluded that higher tirzepatide doses give higher weight reductions.

Additional analyses provided by the company after consultation improved confidence in the clinical- and cost-effectiveness evidence. The cost-effectiveness estimates are within the range that NICE considers an acceptable use of NHS resources. So, tirzepatide is recommended for routine use in the NHS.

To date there are no published cardiovascular outcome trials for tirzepatide. Trials are still ongoing and due to be published in 2025.

Patient safety

- The product should be used within its product licence.
- Tirzepatide is Black Triangle drug. All suspected adverse reactions should be reported to identify any adverse effects.
- The NICE committee acknowledged that the adverse effects of tirzepatide are aligned with those of GLP-1 RAs and expect them to be manageable in clinical practice.

- A National patient safety alert was issued in July 2023[3]. There are very limited, intermittent supplies of all glucagon-like peptide-1 receptor agonists (GLP-1 receptor agonists). Supplies are not expected to stabilise to meet full market demand until at least mid-2024. This means:
    - Many patients cannot source their GLP-1receptor agonist and have to optimise their medications without use of a GLP-1 receptor agonist.
    - New patients cannot be initiated on GLP- 1 receptor agonists.
    - Existing patients should not be switched between brands of GLP-1 RAs, including between injectable and oral forms.
    - It is not recommended to double up a lower dose preparation where a higher dose preparation of GLP-1 RA is not available.
- A further National Patient Safety Alert was issued, 3rd January 2024, with an update to the ongoing supply issues for the GLP-1 RAs.
    - Rybelsus® (semaglutide) tablets are now available in sufficient quantities to support initiation of GLP- 1 RA treatment in people **with type 2 diabetes (T2DM)** in whom new initiation of GLP-1 RA therapy would be clinically appropriate.

- Byetta® (exenatide) 5micrograms/0.02ml and 10micrograms/0.04ml solution for injection 1.2ml pre-filled pens **will be discontinued in March 2024**.
- Victoza® (liraglutide) continues to be out of stock and further stock is not expected until end of 2024.
- The supply continues to be limited, with supply not expected to return to normal until at least the end of 2024.

- Falsified Ozempic and Saxenda products have been found in the UK, including falsified pens containing insulin, which may lead to patient harm. The MHRA advised that the public only obtain prescription-only medicines from legal pharmacies and with a prescription from a qualified healthcare professional[4].

Patient factors

- Patients must adhere to the storage requirements: Tirzepatide should be stored in its original package to protect it from light and stored in a refrigerator. A Tirzepatide pre-filled pen that is being used may be stored unrefrigerated for up to 30 cumulative days at a temperature not above 30 °C and then the pre-filled pen must be discarded.
- Patients would need to be reviewed on a regular basis by the prescribing clinician to ensure concordance and monitoring for adverse effects and efficacy.
- The availability of the tirzepatide device for patient use remains uncertain, consequently delaying the firming up of implementation plans at this time.
- The licence for tirzepatide is for an autoinjector similar to that of the GLP-1 receptor agonists.
- **TO NOTE**:
  - Since the NICE TA was published, the MHRA has now approved the new pen device which is a Kwik Pen device. It is the same as the one used for insulin delivery.
  - There is now availability of stock from February 12th, 2024.
  - The manufacturer assures that current stock is sufficient to fulfil the uplift needed for the GLP-1RA shortages.

Environmental impact

- The new KwikPen device will have a negative environmental impact with regards to waste management. Currently, there the manufacturer is not undertaking a recycling project for the KwikPen devices.
- Discharge into wastewater (post metabolism unknown effect)
- Any device that delivers a subcutaneous injection of tirzepatide would produce sharps waste which requires safe collection and disposal.

Equality & diversity

Equality Impact Assessment:

Protected characteristics Protected Characteristics - Information	**Describe any considerations or concerns for each group.**	**Describe suggested mitigations to reduce inequalities.**
Age	Only licensed for adult patients – younger patients will not be able to access this treatment under this TA.	See note 1 below.
Disability	Patient with learning or physical disabilities may not be able to	Patients will require assistance from provider organizations so

	self-inject and would need support	that district nurses can support them with injections, as is the case with current GLP-1RAs.
Gender reassignment	n/a	
Marriage and civil partnership	n/a	
Pregnancy & maternity	There is a limited amount of data from the use of tirzepatide in pregnant women. It is unknown whether tirzepatide is excreted in human milk.	Tirzepatide should not be used during pregnancy. 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.
Race	Diabetes UK identified the following equality issues: • people of South Asian, Black Caribbean, Black African and South Asian family background are at a higher risk of being diagnosed with type 2 diabetes, and at a younger age	Lower BMI thresholds can be used (usually reduced by 2.5 kg/m2) for people from South Asian, Chinese, other Asian, Middle Eastern, Black African, or African-Caribbean family backgrounds.
Religion and belief	This drug is of biologic origin. It is also worth pointing out that no medicines are 100% vegan friendly as they will have been tested on animals at some point.	People using tirzepatide should be made aware of this in case this affects their beliefs.
Sex	n/a	
Sexual orientation	n/a	
Impact on any other vulnerable groups?	. • there is a higher prevalence of the condition among people in more deprived areas and they have poorer care, leading to poorer outcomes. • a high proportion of people with type 2 diabetes have excess weight. People who experience weight stigma are less likely to have good care and to seek help from a healthcare professional to	The NICE committee noted these concerns but concluded that they had no effect on its recommendations.

	support weight loss	

Note 1: Drugs approved by NICE for adult conditions will be commissioned in children at specialised paediatric centres if the patient meets the NICE criteria and there is evidence to suggest that the drug is safe and clinically appropriate to use in children as per the NHS England Medicines for Children Policy (see https://www.england.nhs.uk/publication/commissioning-medicines-for-children-specialised-services/ and a Blueteq form is available.

Place in therapy relative to available treatments

NICE have placed Tirzepatide in the same position as GLP-1 receptor agonist drugs. (see link below to NICE guidance NG28)

NG28 Visual summary on choosing medicines for type 2 diabetes in adults (nice.org.uk)

The main difference in the management of patients using tirzepatide, a GIP/GLP-1 medication, to GLP-1 receptor agonist drugs, lies in the absence of a review recommendation by NICE, for tirzepatide.

Currently NICE recommend the following review for GLP-1 receptor agonists:
'It is recommended that patients should be reviewed six months after GLP-1 initiation. If the patient has not had a 11mmol/mol reduction in HbA1c AND a 3% reduction from baseline weight, then the GLP-1 receptor agonist should be discontinued.'

Stakeholder views

The paper was sent out for consultation and comments are listed on the front sheet.
Comments included in the front sheet.
Comments

Cost-effectiveness (1)

Section 1: cost of the technology

a. Price of Tirzepatide relative to comparable medicines:

Dose of Tirzepatide	Cost to prescribe for 28 days	Cost to prescribe per year
2.5mg and 5mg	£92	£1,196
7.5mg and 10mg	£107	£1391
12.5mg and 15mg	£122	£1586

Drug and Dose	Medicine to prescribe by brand name	Quantity to prescribe for 28 days	Cost to prescribe for 28 days*
Liraglutide 1.2mg daily#	Victoza® 6mg/ml solution for injection, 3ml pre-filled pen	1 box 2 pens for 30 days supply (each pen contains 15 doses)	£78.48
Liraglutide 1.8mg daily#	Victoza® 6mg/ml solution for injection, 3ml pre-filled pen	3 pens for 30 days supply (each pen contains 10 doses)	£117.72
Dulaglutide 0.75mg WEEKLY	Trulicity® 0.75mg/0.5ml solution for injection, pre-filled pen	1 box of 4 pens (each pen contains 1 dose)	£73.25
Dulaglutide 1.5mg WEEKLY	Trulicity® 1.5mg/0.5ml solution for injection, pre-filled pen	1 box of 4 pens	£73.25
		(each pen contains 1 dose)	
Dulaglutide 3mg WEEKLY	Trulicity® 3mg/0.5ml solution for injection, pre-filled pen	1 box of 4 pens (each pen contains 1 dose)	£73.25
Dulaglutide 4.5mg WEEKLY	Trulicity® 4.5mg/0.5ml solution for injection, pre-filled pen	1 box of 4 pens (each pen contains 1 dose)	£73.25
Semaglutide 0.25mg WEEKLY	Ozempic®)0.25mg/0.19ml solution for injection, 1.5ml pre-filled pen	1 Box of 1 Pen **(Each Pen contains 4 doses)**	£73.25
Semaglutide 0.5mg WEEKLY	Ozempic® 0.5mg/0.37ml solution for injection, 1.5ml pre-filled pen	1 Box of 1 Pen **(Each Pen contains 4 doses)**	£73.25
Semaglutide 1.0mg WEEKLY	Ozempic® 1mg/0.74ml solution for injection, 3ml pre-filled pen	1 Box of 1 Pen **(Each Pen contains 4 doses)**	£73.25
Semaglutide 3mg or 7mg or 14mg	Rybelsus® 14mg, 7mg or 3mg tablets box of 30	1 box of 30 tablets	£78.48

Drug tariff NOV 23: https://www.nhsbsa.nhs.uk/pharmacies-gp-practices-and-appliance-contractors/drug-tariff

Section 2: NICE resource impact statement and template

a. NICE resource impact statement[5]

All ICERs produced in the scenario analyses were less than £20,000 per QALY. gained for tirzepatide. So, the NICE committee considered tirzepatide to be a cost-effective use of NHS resources. It recommended tirzepatide in line with the company's positioning, that is, as an alternative to GLP-1 RAs in the type 2 diabetes treatment pathway.

b. NICE resource impact template[6]:

Cost of adding tirzepatide to the Type 2 diabetes clinical pathway.

Eligible population	% of people	Current number of people	% of people	Number of people in 5yrs
Adult population Current		817,850		
Adult population forecast at 2028/29				851,080
Prevalence of diabetes	4.30%	36,596	4.70%	40,001
Prevalence of type 2 diabetes	90%	32,937	90%	36,001
Proportion of people receiving pharmacological treatment for type 2 diabetes	71.50%	23,550	71.50%	25,741
Proportion of people eligible for GLP-1 receptor agonists	8.35%	1,966	8.35%	2,149
Eligible population		1,966		2,149
Cost of patients		**£1,915,385** Cost of all patients on GLP-1s		**£2,169,512** Cost in 5 yrs **of all** GLP-1s including all NEW patients maintained on tirzepatide 7.5mg/10mg

Tirzepatide, in this particular indication, does not introduce a new patient group but is priced higher compared to existing medications occupying the same position within the treatment pathway.

If all new patients were to be initiated with tirzepatide at maintenance dose of 7.5mg/10mg, the increased drug costs in Surrey Heartlands are below £100,000 per population at £22,340 at 5 years.

The NICE resource impact template seems to underestimate the number of people who are currently using GLP-1s. From ePACT data, before the GLP-1 shortages occurred in Dec22-May23, there were around 5,185 patients who were using GLP-1-RAs.

Using this data, the increased drug costs still **do not** hit the threshold for £100,000 per place per annum cost pressure in 5 years.

Traffic light recommendation to APC

NHS Payment Scheme (NHSPS) excluded high-cost drug: see NHS England » 2023-25 NHS Payment Scheme

Recommended traffic light status:

1. Added as GREEN (see narrative):

   Dulaglutide remains the preferred choice among GLP-1 options for weekly injections and semaglutide stands as an alternative to dulaglutide for weekly injections.

   Please consider tirzepatide as a third line option to dulaglutide and semaglutide weekly injection, **only** if:
   - dulaglutide and semaglutide are unsuitable.

   or
   - the supply of dulaglutide and semaglutide weekly injections is unavailable.

Rationale:

- NICE have placed Tirzepatide in the same position as GLP-1 receptor agonist drugs in the treatment pathway for patients with type 2 diabetes.
- Trial evidence shows that this group of drugs is similar in effectiveness to GLP-1RAs with a similar adverse events profile.
- Tirzepatide maintenance dose costs 40% more than semaglutide and dulaglutide at £107/mth vs £73/mth.
- There is a lack of trial evidence for cardiovascular outcomes for tirzepatide, but trials are ongoing and expected to publish 2025.
- Unlike the GLP-RAs, NICE has not recommended a review period for tirzepatide.
- Tirzepatide can offer a solution for the supply issues with GLP_1RAs. This can be an alternative to GLP-1RAs for patients unable to source their GLP-1RA or for new patients. The global and national GLP-1 shortage is anticipated to continue until at least end of 2024. The manufacturer gives assurance that tirzepatide can maintain the uplift needed for the GLP-1 shortage.

Implementation

NICE TA implementation must be within 90 days of publication.

Actions to implement:

a. Primary care:
   - Communication email to all to clinicians about Tirzepatide and its place in therapy.
   - Recorded webinar about prescribing points for tirzepatide.
   - Demonstration devices to be distributed to clinicians in primary and secondary care. The manufacturer will send out demonstration devices via the local Lilly representative. The website can be used to educate patients with videos and online information. Secondary care:
- NHS hospital trusts to follow internal governance procedures to add to their formulary and make available for prescribing.
- The initiation, administration and on-going treatment can be managed by primary or

secondary care depending on the needs of the patient.

b. PAD and Joint Formulary:
Surrey PAD documents to be reviewed and updated to include tirzepatide in the same position as GLP-1 receptor agonists.
- Blood glucose control - Treatment algorithm - June 2022.pdf
- Diabetes Type 2 - Treatment guidelines - update June 2022.pdf
- Hypoglycaemic agents -Preferred choices - Update June 22.pdf

Proposed tick box forms

N/A

References:

1) Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/14203/smpc#gref Accessed 28.11.23
2) NICE Technology Appraisal Guidance: Available at: https://www.nice.org.uk/guidance/ta924
3) National Patient Safety Alert: Available at: https://www.sehd.scot.nhs.uk/publications/DC20230718Agonists.pdf Accessed 28.11.23
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5) NICE Resource Impact Report: Available at: https://www.nice.org.uk/guidance/ta924/resources/resource-impact-report-pdf-13242144349 . Accessed 28.11.23
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Declaration of interest:

	Name	Role	Date	Declaration of interests (please give details below)
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None.

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1			Draft	Out for consultation
			Final	Out for clinical comment