Review proposal of semaglutide for managing overweight and obesity [TA875 and TA910]

Review proposal outcome

This document outlines the review proposal and outcome for semaglutide for managing overweight and obesity in adults (TA875) and in young people aged 12 to 17 years (TA910). The proposal included incorporating the licence extension of semaglutide for preventing cardiovascular events in people with cardiovascular disease and overweight or obesity into the evaluation, if updated. See appendix A for details of the review proposal.

Following a written consultation and stakeholder workshop on this proposal, the outcome is as follows:

- a single technology appraisal (STA) for semaglutide for preventing major cardiovascular events in people with cardiovascular disease and overweight or obesity (ID6441) is to be scheduled into the work programme,
- TA875 will not be updated at this time, but this decision should be reconsidered alongside the surveillance review of TA1026.
- TA910 will not be updated at this time, but this decision should be reconsidered alongside the surveillance review of TA1026

Summary of stakeholder engagement

Proposal to update TA875

Stakeholders would welcome re-evaluation of the 2-year stopping rule and setting (specialist weight management services) specified in TA875. Clinicians and commissioners highlighted the difficulty with both aspects, which confuses the treatment pathway (in the context of tirzepatide being available in primary care with no stopping rule according to TA1026) and is difficult to implement in practice.

There is unlikely to be any new evidence which would change the clinical or cost effectiveness of semaglutide if TA875 was updated. The company proposed adoption of semaglutide into primary care in line with the implementation plan for TA1026 'Tirzepatide for managing overweight and obesity'. This would allow real-world evidence on the effectiveness of semaglutide to be collected over the 3-year review period specified in the implementation plan for tirzepatide, with a review of cost-effectiveness of semaglutide at that time.

Incorporating the cardiovascular disease indication into an update of TA875

There are defined treatment pathways for cardiovascular event prevention in people with established cardiovascular disease. Most people with cardiovascular disease are treated in secondary care initially, and managed long-term in primary care. The clinical community would welcome a simplification of the delivery pathway for semaglutide, which is currently very complex for management of obesity. This would be best achieved by keeping semaglutide for cardiovascular disease in a separate pathway for prevention of cardiovascular disease. Attempting to incorporate cardiovascular management with semaglutide into overweight and obesity management pathways would be problematic.

Most participants (71%) in the key clinical trial for cardiovascular outcomes (SELECT) had a body mass index (BMI) of less than 35 kg/m^2. So, the evidence for cardiovascular risk is not representative of the population who are currently eligible for semaglutide in TA875.

There is evidence of cardiovascular benefits of semaglutide unrelated to weight loss and across different BMI cohorts, through an unknown mechanism of action. Clinicians would value the option to offer semaglutide to people who meet the criteria for cardiovascular risk, at a lower BMI threshold than recommended for weight loss.

By combining the cardiovascular risk indication with TA875, there is a risk that the benefits of semaglutide for the cardiovascular risk population will not be fully accounted for. It is anticipated that multiple economic models would be required for a combined review which covers the different populations and outcomes of interest for each indication.

Incorporating young people into an update of TA875

Accessing semaglutide for young people is difficult in practice. Stakeholders anticipate that a NICE recommendation for semaglutide for young people with overweight or obesity would aid access for people who are treated in specialist services, who currently have no pharmacological treatment options.

The company agreed that a submission for young people would be possible as part of a review of TA875. But, it noted there will be high levels of uncertainty in economic

modelling. There are no risk equations available specifically for young people and extrapolation of outcomes will be required for a longer period than for the adult population.

Conclusion on review proposal

The clinical pathway for cardiovascular disease prevention, in particular treatment setting and comparators, is distinct from the pathway for management of obesity. The evidence (population and outcomes) for semaglutide for cardiovascular event prevention is also distinct from the evidence for semaglutide for weight loss. Stakeholders raised concerns about additional complexity of incorporating semaglutide for its cardiovascular indication into a weight management pathway. So, it is not appropriate to incorporate the cardiovascular disease indication into an update of TA875.

There is unlikely to be any new evidence for semaglutide for managing overweight and obesity to inform an update of TA875. It cannot be assumed without economic evaluation that semaglutide would continue to be cost effective in a primary care setting, without a stopping rule. Therefore, any changes to the recommendation to change the treatment setting or stopping rule would require a review of TA875. Given the surveillance review of TA1026 ‘Tirzepatide for managing overweight and obesity’ planned for 3 years following publication, and the decision not to incorporate the cardiovascular disease indication into an update of TA875, it is proportionate to consider a review of TA875 at the same time.

Given the conclusion to not update TA875 at this time, it is not proportionate to review TA910. This should also be reconsidered alongside the planned review of TA1026.

Appendix A - Review proposal

TA875 and TA910 were published in 2023.

A review of the guidance should be planned into the appraisal work programme with an expanded objective to include the appraisal of semaglutide for the reduction of major adverse cardiovascular events in people with established cardiovascular disease and either overweight or obesity.

The review will be conducted through the STA process.

That we consult on this proposal alongside a consultation on a draft scope for this appraisal.

Rationale

TA875 considered the clinical and cost-effectiveness of semaglutide within its marketing authorisation at the time: that is as an adjunct to a reduced-calorie diet and increased physical activity for adults with an initial BMI of ≥30 kg/m^2 (obesity) without co-morbidity, or ≥27 kg/m^2 to <30 kg/m^2 (overweight) in the presence of at least one weight-related comorbidity. TA910 is a terminated appraisal: NICE was unable to make a recommendation on semaglutide for managing overweight and obesity in young people aged 12 to 17 years because the company did not provide an evidence submission. An update to the guidance would give the opportunity for the clinical and cost-effectiveness in younger people to be appraised as part of the broader appraisal.

TA875 recommends semaglutide as an option for weight management, including weight loss and weight maintenance, alongside a reduced-calorie diet and increased physical activity in adults, only if:

- it is used for a maximum of 2 years, and within a specialist weight management service providing multidisciplinary management of overweight or obesity (including but not limited to tiers 3 and 4), and
- they have at least 1 weight-related comorbidity and:
  - a body mass index (BMI) of at least 35.0 kg/m^2, or
  - a BMI of 30.0 kg/m^2 to 34.9 kg/m^2 and meet the criteria for referral to specialist weight management services in NICE's guideline on obesity: identification, assessment and management
- the company provides semaglutide according to the commercial arrangement.

Since the publication of TA875 and TA910, the marketing authorisation for the Wegovy brand of semaglutide has been extended. In July 2024, it was granted a marketing authorisation in the UK ‘as an adjunct to a reduced-calorie diet and

increased physical activity to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with established cardiovascular disease and either obesity or overweight (BMI ≥ 27 kg/m^2)'.

People with cardiovascular disease and obesity or overweight form a subset of the population covered in the appraisal that resulted in the TA875 guidance. However, the recommendations in TA875 limit the use of semaglutide to weight management services, limit the duration of treatment to 2 years and the nature of the commercial arrangement means that it is only available in secondary care settings at present. Furthermore, continuation of treatment must be reconsidered if less than 5% of the initial weight has been lost after 6 months of treatment. This may not be appropriate when the technology is used for cardiovascular prevention.

As a consequence of the above, a significant proportion of people eligible for treatment under the cardiovascular prevention indication would not be able to access semaglutide in an appropriate setting and for an appropriate duration under current guidance on semaglutide for the treatment of overweight and obesity. However, there is a broader question about whether the current guidance remains appropriate in the light of recent developments including the publication of guidance on the use of tirzepatide (TA1026) which does not specify the setting in which tirzepatide should be used.

The principal aim of treatment of obesity is to reduce the adverse effects of the condition on health. This includes the impact of obesity on hypertension, hypercholesterolaemia, and diabetic/non-diabetic hyperglycaemia, all of which increase the risk of major adverse cardiovascular events. Based on this, it is considered appropriate to consider established cardiovascular disease alongside other comorbidities in a broader appraisal of the clinical and cost-effectiveness of semaglutide in people with overweight (with comorbidities) or obesity.

Summary of new evidence and implications for review

The technology

The recommendations in TA875 were mainly based on a randomised double-blind trial that compared a semaglutide once-weekly injection with placebo alongside lifestyle interventions (STEP-1). It included adults with obesity (BMI of 30.0 kg/m^2 or more) with or without a comorbidity, or with overweight (BMI of 27.0 kg/m^2 to 29.9 kg/m^2) with at least 1 weight-related comorbidity. The comorbidities included hypertension, dyslipidaemia, obstructive sleep apnoea or cardiovascular disease. People with type 2 diabetes were excluded from the trial.

The update to the marketing authorisation to include cardiovascular prevention in people with overweight or obesity is based on a randomised controlled trial of semaglutide compared with placebo in adults aged 45 years or older with

cardiovascular disease and a BMI of 27 or more (SELECT). People with Type 1 and Type 2 diabetes were excluded. The effects of semaglutide on cardiovascular outcomes have also been studied in a randomised controlled trial compared with placebo in adults with insufficiently controlled type 2 diabetes (SUSTAIN 6).

Has there been any change to the price of the technology(ies) since the guidance was published?

The Wegovy brand of semaglutide has a commercial arrangement.

Liraglutide, the first GLP-1 agonist to be licensed for the treatment of obesity and overweight, has lost market exclusivity and is now available from other companies. In time, competition may reduce the price of this comparator medicine.

Are there any existing or proposed changes to the marketing authorisation that would affect the existing guidance?

Semaglutide is in topic selection for treating non-alcoholic steatohepatitis with significant liver fibrosis, which is an obesity-related condition. Depending on the timing of the marketing authorisation, this comorbidity could also be included in the update.

Were any uncertainties identified in the original guidance? Is there any new evidence that might address this?

The STEP-1 trial did not include people with type 2 diabetes. The Ozempic brand of semaglutide is licensed for the treatment of type 2 diabetes, but the maximum recommended dose is lower than that for the Wegovy brand that is indicated for the treatment of overweight and obesity. NICE guideline 28 'Type 2 diabetes in adults: management' recommends considering switching one component of a triple oral regimen for a GLP-1 mimetic when the triple therapy with metformin and 2 other oral drugs is not effective, not tolerated or contraindicated. This recommendation applies to adults who:

- have a BMI of 35 kg/m^2 or higher (adjusted accordingly for people from Black, Asian and other minority ethnic groups) and specific psychological or other medical problems associated with obesity or
- have a BMI lower than 35 kg/m^2 and:
    - for whom insulin therapy would have significant occupational implications or
    - weight loss would benefit other significant obesity-related comorbidities.

People with type 2 diabetes and obesity may be eligible for semaglutide for weight management as well as under the diabetes recommendation. The cost-effectiveness of semaglutide for weight management in a population with type 2 diabetes was not assessed in TA875 because it was based on the STEP-1 trial. The

committee agreed that this introduced some uncertainty about the generalisability of the clinical effectiveness results, and may have affected the reliability of the cost-effectiveness results to the broader population who might be offered semaglutide in the NHS.

Are there any related pieces of NICE guidance relevant to this appraisal? If so, what implications might this have for the existing guidance?

NICE has a guideline on overweight and obesity management (NICE guideline 246). This incorporates existing NICE technology appraisal guidance on medicines for treating overweight and obesity. Any update to TA875 would entail a corresponding amendment to the guideline.

Questions for consultation

Is an update of TA875 appropriate at the present time?

Is it appropriate to consider the population with established cardiovascular disease within a broader appraisal of semaglutide for overweight and obesity?

Should people with type 2 diabetes be considered within this appraisal of the overweight and obesity indication? Is there sufficient evidence to support a recommendation for this group specifically?

Is it appropriate to include the indication for semaglutide for managing overweight and obesity in young people aged 12 to 17 years in this update?

NICE intends to evaluate this technology through its Single Technology Appraisal process. (Information on NICE's health technology evaluation processes is available at https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/changes-to-health-technology-evaluation).

Equality issues

People from some minority ethnic family backgrounds are at an equivalent risk of the consequences of obesity at a lower BMI than people from a White ethnic family background. NICE's guidance recommends using lower BMI thresholds for South Asian, Chinese, other Asian, Middle Eastern, Black African or African-Caribbean family backgrounds when identifying the risk of developing type 2 diabetes and providing interventions to prevent it.

Proposal/decision paper sign off

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Appendix B – Information from existing guidance

Original remit

To appraise the clinical and cost effectiveness of semaglutide, within its marketing authorisation, in addition to a reduced calorie diet and increased physical activity, for the management of people with obesity or overweight with risk factors.

Current guidance

1.1 Semaglutide is recommended as an option for weight management, including weight loss and weight maintenance, alongside a reduced-calorie diet and increased physical activity in adults, only if:

- it is used for a maximum of 2 years, and within a specialist weight management service providing multidisciplinary management of overweight or obesity (including but not limited to tiers 3 and 4), and
- they have at least 1 weight-related comorbidity and:
- a body mass index (BMI) of at least 35.0 kg/m^2, or
- a BMI of 30.0 kg/m^2 to 34.9 kg/m^2 and meet the criteria for referral to specialist weight management services in **NICE's guideline on obesity: identification, assessment and management**.
- the company provides semaglutide according to the **commercial arrangement**.

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.

1.2 Consider stopping semaglutide if less than 5% of the initial weight has been lost after 6 months of treatment.

1.3 These recommendations are not intended to affect treatment with semaglutide that was started in the NHS before this guidance was published. People having treatment outside these recommendations 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.

Research recommendations from original guidance

N/A

Appendix C – Explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below

Options	Consequence	Selected – 'Yes/No'
A review of the guidance should be planned into the appraisal work programme. The review will be conducted through the STA process.	A review of the appraisal will be planned into the NICE's work programme.	Yes
The decision to review the guidance should be deferred to specify date or trial.	NICE will reconsider whether a review is necessary at the specified date.	No
The guidance should be Cross referred into an on-going clinical guideline.	The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review. This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.	No
The guidance should be updated in an on-going clinical guideline[1].	Responsibility for the updating the technology appraisal passes to the NICE Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn. Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).	No

[1] Information on the criteria for NICE allowing a technology appraisal in an ongoing clinical guideline can be found in section 6.20 of the guide to the processes of technology appraisal.

Options	Consequence	Selected – 'Yes/No'
The guidance remains relevant, and an update is not needed.	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider.	No
The guidance should be withdrawn	The guidance is no longer relevant and an update of the existing recommendations would not add value to the NHS. The guidance will be stood down and any funding direction associated with a positive recommendation will not be preserved.	*No*