For projector/publication – No ACIC

NICE National Institute for Health and Care Excellence

Semaglutide for managing overweight and obesity

Chair presentation

Lead Team: Abdallah Al-Mohammad, Richard Ballerand, G.J. Melendez-Torres

ERG: Southampton Health Technology Assessments Centre

Chair: Jane Adam

Technical team: Albany Meikle, Joanna Richardson, Janet Robertson

Company: Novo Nordisk

March 15 2022

Key issues following consultation

- Concerns around implementation in tier 3 services associated with tier 3 service distribution across the country – **consideration of treatment setting**
- Inclusion of **2 year stopping rule**
- Uncertainty for **time to regain weight** following discontinuation
- Uncertainty around use of **retreatment**
- Use of **risk equations** for a time limited intervention to predict long term cardiovascular outcomes
- Consideration of **specific populations**:
  - People with severe mental illness (for whom access to tier 3 services is limited)
  - People who have had previous bariatric surgery (different modelling may be required to estimate cost effectiveness in this population)
  - People who may particularly benefit from semaglutide (people who need to lose weight for surgery or to start IVF; people who are planning pregnancy; people with diabetes)
- **Wording of recommendations**:
  - Term ‘exceptionally’ for referral of people with BMI 30 to 34.9 kg/m2
  - Defining weight-related comorbidity in the recommendation
  - Providing a clear BMI threshold for people from south Asian, Chinese, and Black African or Caribbean family backgrounds
- **Stopping rule for people who lose <5% body weight at 6 months**
- **Uncertainty around use compared with bariatric surgery**
- **Are there any uncounted benefits not captured by the QALY calculation?**

Treatment setting

- Tier 3 services are usually accessed by people with BMI ≥35 + ≥1 comorbidity, although criteria for considering referral to tier 3 services for people with BMI 30 to 34.9 are recommended in NICE's clinical guideline on obesity (~1.5% of people in tier 3 services have BMI 30 to 34.9)
- Tier 3 referral is for up to 2 years (although time limit not specified in NHS national guidance)
- Tier 3 services are not available in all areas of the country, although equivalent services may exist, not called tier 3
- Economic model is based on company model used for liraglutide appraisal. Liraglutide is recommended in tier 3 only, and model assumptions reflect tier 3 service because only these (or equivalent) last longer than 12 weeks and have multidisciplinary input. Clinical experts did not consider that this could be a stand-alone treatment

Company's cost effectiveness model

- **Cohort transition model** 11 health states (from model for liraglutide (TA664))
- Treatment effects from the full population of STEP 1
- Company target population (BMI ≥30 + ≥1 comorbidity): 53.4% enter model with pre-diabetes; based on prevalence in STEP 1
- Liraglutide eligible population (BMI ≥35 + pre-diabetes + CVD risk): 100% enter model with pre-diabetes
- Risk equations using surrogate outcomes used to calculate risk of acute cardiovascular event (based on BMI, systolic blood pressure, total cholesterol, HDL cholesterol and HbA1c) and risk of developing type 2 diabetes (based on BMI and HbA1c levels)
  - Model includes improvement in outcomes over 2 years followed by return to baseline at 5 years (risk equations are usually applied to a steady state improvement in outcomes)
- Fatal event risk based on disease specific and general population mortality

NICE

Abbreviations: BMI – body mass index; HDL – high density lipoprotein; CVD – cardiovascular disease

Draft recommendation

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:

- **they have at least 1 weight-related comorbidity and:**
  - **a body mass index (BMI) at least 35.0 kg/m^2, or**
  - **exceptionally, a BMI of 30.0 kg/m^2 to 34.9 kg/m^2 if they are referred to tier 3 services based on the criteria in NICE's clinical guideline on obesity: identification, assessment and management.**

Based on relevant subgroup in trial

Population eligible for tier 3 services
'Exceptionally' reflects the limited criteria for tier 3 eligibility in CG189

Use lower BMI thresholds (usually reduced by 2.5kg/m^2) for people from south Asian, Chinese, and Black African or Caribbean family backgrounds.

1.2 Prescribe semaglutide as part of a specialist weight management service with multidisciplinary input (such as a tier 3 or tier 4 service).

Based on evidence, clinical expert opinion and marketing authorisation that semaglutide should be offered alongside diet and exercise, which is structured and assessed in specialist weight management services (example of tier 3 or 4 services as these are not available ubiquitously nationwide)

1.3 Only use semaglutide for a maximum of 2 years.

Based on time spent in tier 3 services and treatment course used in model

≥ 30 kg/m^2 **or** ≥ 27 kg/m^2 to < 30 kg/m^2 in the presence of at least one weight-related comorbidity

Full marketing authorisation population

≥30 kg/m^2 and ≥1 weight-related comorbidity

Company's target population

≥35 kg/m^2 and ≥1 weight-related comorbidity **or** 30 to 34.9 kg/m^2 and ≥1 weight-related comorbidity **plus** meet referral criteria for tier 3 services in CG189

Draft recommendation population

Not all people with BMI 30 to 34.9 are eligible for tier 3 (see criteria in CG189) = a restriction on company's target population

CG189:

Consider referral to tier 3 services if:

- the underlying causes of being overweight or obese need to be assessed
- the person has complex disease states or needs that cannot be managed adequately in tier 2 (for example, the additional support needs of people with learning disabilities)
- conventional treatment has been unsuccessful
- drug treatment is being considered for a person with a BMI of more than 50 kg/m^2
- specialist interventions (such as a very-low-calorie diet) may be needed
- surgery is being considered.

Why the committee made these recommendations:

- Semaglutide is cost effective compared with liraglutide
  - recommended for liraglutide eligible subgroup
- ICERs for semaglutide compared with diet and exercise are uncertain, so appropriate to recommend for people who are at the highest risk for the adverse events of obesity and likely to gain the most benefit: a restricted version of the company's target population
  - Company and ERG base case are under £20,000 per QALY gained
  - Mean starting BMI in model may be higher than in the population who would be eligible for semaglutide - ICER increases when mean starting BMI is decreased
  - Uncertainty around average time to weight regain – ICER increases when assuming weight regain over 1 or 2 years (rather than 3 in base case)
  - Uncertainty around percentage with type 2 diabetes who would be treated in practice – ICER increases when people with type 2 diabetes included in model
  - Uncertainty around use of risk equations for estimating long term cardiovascular benefits

Abbreviations: CVD – cardiovascular disease; ICER – incremental cost effectiveness ratio; QALY – quality-adjusted life year

Draft recommendation in relation to clinical evidence available

- No trial evidence of efficacy if used outside specialist weight management service
  - marketing authorisation specifies semaglutide use alongside diet and exercise
  - company and clinical experts do not consider semaglutide a ‘stand-alone’ treatment but part of a focused treatment package
- No trial evidence of long-term efficacy
  - maximum use in trial was 68 weeks so weight and other long term outcomes are unknown

Evaluation of long term maintenance use would require more clinical trial evidence on efficacy (to show waning of effect, as seen in bariatric surgery long term), use outside a dedicated weight management service and incorporation of different costs depending on setting. None of this evidence is currently available.

Current management

- Tier 2 services include community based diet, nutrition, lifestyle and behaviour change advice for 12 weeks
- Tier 3 services include clinician led multidisciplinary team specialist weight management including interventions from specialist physicians, psychologists, dieticians, specialist nurses, psychiatrists and physiotherapists
- Tier 3 usually accessed by people with BMI ≥35 kg/m^2 (or lower BMI if significant comorbidities, with adjustment for ethnicity) plus ≥1 comorbidity
  - in line with NICE quality standard 127 (based on CG189), adults with BMI ≥30 for whom tier 2 interventions have been unsuccessful should discuss alternative interventions including tier 3 services
  - **company target population (BMI ≥30 + 1 comorbidity) would not all be treated in tier 3**
  - liraglutide is only available in tier 3
  - not all CCGs commission tier 3 services
- Tier 4 services includes multidisciplinary team weight management programmes and where appropriate bariatric surgery

STEP 1 results: BMI ≥ 30 kg/m² plus at least 1 comorbidity (company's target population)

Diet and exercise is considered standard of care for this population
Results from STEP 1 trial (75% of trial population):

Outcome	Semaglutide 2.4mg + diet and exercise	Placebo + diet and exercise	Treatment difference
Baseline to week 68			
Change in % body weight, mean (SD)	-14.8 (8.8)	-2.6 (8.8)	-12.2
Proportion shifting from non-diabetic hyperglycaemia to normo-glycaemic, %	79.2	20.0	59.2
Systolic blood pressure, mmHg, mean (SD)	-6.4 (12.1)	-1.0 (12.1)	-5.4
HbA1C, mean (SD)	-0.5 (0.3)	-0.1 (0.3)	-0.4
HDL cholesterol, mg/dL, mean (SD)	0.0 (0.1)	0.0 (0.1)	0
Total cholesterol, mg/dL, mean (SD)	0.0 (0.1)	0.0 (0.1)	0

Suggests that semaglutide prolongs time without diabetes

NICE

Abbreviations - BMI: body mass index; SD: standard deviation; HDL: high density lipoprotein

Model assumptions – overview of conclusions from ACM1

ACD: the model is "only suitable for decision making for treatment in specialist weight management services" – assumptions included are based on use in specialist weight management services. Base case assumes 2 year treatment duration (model allows max 3 year treatment duration)

Assumption	Company justification	Committee conclusions in ACD
Stopping rule: for people who have not lost at least 5% of initial body weight at 6 months to discontinue treatment	MA: "If patients have been unable to lose at least 5% of their initial body weight after 6 months on treatment, *a decision is required on whether to continue treatment*…"	Accepted stopping rule – in line with clinical expert opinion and the marketing authorisation
Treatment duration max 2 years	Aligns with time spent in tier 3 services	Not ideal, but reasonable in the context of using semaglutide in tier 3 services, which is limited to 2 years
No retreatment throughout full time horizon	No evidence available to support 'stop and re-start' treatment pattern	Retreatment may be appropriate for some people
Weight regain to baseline after 3yrs	Reflects natural progression when treatment is stopped	Area of significant uncertainty – no evidence to support weight regain over 3 years; large impact on ICER
100% with non-diabetic hyperglycaemia develop T2D after CVD event	Simplifying assumption; no risk equation available to predict CVD risk for people with non-diabetic hyperglycaemia	Likely 100% is an overestimation of proportion who develop T2D after a CVD event; limited impact on ICER
Risk equations to estimate CVD and diabetes events	Based on surrogate outcomes in STEP 1	No practical alternative; may be that short term improvement in weight and risk factors provides long term benefit, but no evidence; large impact on ICER

MA: marketing authorisation; T2D – type 2 diabetes; CVD – cardiovascular disease; ICER – incremental cost effectiveness ratio; ACD – appraisal consultation document

ACD consultation responses

Comments received from:

- NHS England and NHS Improvement (NHSE&I)
- NHSE&I clinical expert
- Novo Nordisk
- Patient experts
- Royal College of Physicians
- Obesity Group of the British Dietetic Association

- Web comments

Tier 3 services

Company:

- Recommendations should refer only to term specialist weight management services, not tier 3

NHS England

- No national recommendation for duration of referral to specialist weight management services

Royal College of Physicians:

- Possible postcode lottery based on availability of tier 3 services and waiting lists for specialist weight management services

Web comments:

- Recommendation will disadvantage half the population who do not have access to tier 3 services; should consider prescription in tier 2 services
- Should be clear if this can be prescribed in a community tier 3 setting
- Restricting prescribing in tiered approach inappropriate as this may be changed in future
- Concerns around implementation of guidance considering the available resources and infrastructure in tier 3 settings – long waiting lists will be formed very rapidly with increased referrals

ACD: recommends semaglutide as part of a specialist weight management service with multidisciplinary input (such as a tier 3 or tier 4 service); for people with a BMI of 30.0 kg/m^2 to 34.9 kg/m^2, semaglutide is recommended if they are referred to tier 3 services based on the criteria in NICE's clinical guideline on obesity

- **Are tier 3 services the only appropriate setting for semaglutide use?**

2 year treatment duration (1)

NHS England

- Time limited access creates an artificial stopping point, not based on clinical evidence
- Evidence that once treatment is stopped, weight is regained, reducing the cost-effectiveness of treatment. Re-referral will reduce cost effectiveness further

Royal College of Physicians

- Obesity is a chronic condition
- Weight regain and worsening or relapse of obesity-related comorbidities associated with stopping treatment is likely to have impact on psychological wellbeing

British Dietetic Association

- Concerns about 2 year treatment length for a chronic condition
- Some tier 3 services are only available for 1 year

Patient experts

- Treatment should be lifelong and concerns about 2 year treatment length
- Long term maintenance treatment for people following bariatric surgery would be beneficial

Web comments:

- It doesn’t make clinical sense to treat a chronic disease for only 2 years
- Stopping treatment at 2 years is not evidence based - evidence that semaglutide is not toxic or ineffective in the long-term so stopping rule not justified
- Major implementation challenges - treatment will not be stopped after 2 years for those benefiting (as seen with liraglutide in practice) – therefore the true cost effectiveness of semaglutide can only be determined by removing the stopping rule

2 year treatment duration (2)

ACD:

- Committee understood that 2-year treatment aligns with time spent in tier 3 services
- Marketing authorisation specifies that semaglutide should be provided alongside lifestyle interventions – clinical experts noted these are provided in specialist weight management services and this is the appropriate setting for semaglutide use
- Not ideal to treat a chronic condition for only 2 years – but model is based on 2 year course of treatment as this reflects how long on average people receive SWMS in tier 3
- Assumption that treatment would be stopped at 2 years reasonable in context of NHS tier 3 services

Clinical expert views on treatment length related to tier 3 services:

- Most tier 3 services offer 2 year treatment (minority offer 12 or 6 months)
- May be very exceptional cases where treatment offered beyond 2 years (outside local policy)
- On average, people attend tier 3 for less than a year; around 20-30% complete 2 years - those who respond best to treatment more likely to stay for full 2 years
    - those who leave before 2 years usually due to poor results or referral for bariatric surgery

	Semaglutide vs diet and exercise	ICER (£/QALY)
Scenario based on ERG base case	ERG base case*	16,337
	Treatment duration: 3 years	17,747

*ERG base case includes 2 year treatment duration

- **Is a 2 year stopping rule for semaglutide appropriate?**

Abbreviations: SWMS – specialist weight management service

Weight regain

Web comments

- SCALE Obesity and Prediabetes trial shows rapid weight regain in first 12 weeks after stopping liraglutide – indicates that all weight advantage of liraglutide would be lost after 6 to 12 months and similar expected for semaglutide
- Assumption of 3 year weight regain isn't evidence based

Royal College of Physicians

- When semaglutide is stopped, people regain the lost weight (shown by STEP 4 trial)

ACD: Area of significant uncertainty – no evidence to support weight regain over 3 years

ERG

- Cautions against extrapolating weight regain at 12 weeks in SCALE trial to longer periods
- STEP 4 provides better evidence of likely weight regain after semaglutide discontinuation:
  - STEP 4 measured weight regain for 48 weeks after 20 weeks of semaglutide treatment (lifestyle interventions continued following semaglutide discontinuation)
  - Shows on average, people who stopped semaglutide did not regain all the weight they had lost within 1 year (note semaglutide treatment length in STEP 4 is shorter than 2 years)
- Company's assumption of weight regain within 3 years is reasonable

Weight regain

Clinical experts:

- Weight regain to baseline estimated to take around 2 to 3 years on average (some will maintain clinically relevant weight loss for longer)
- Weight regain following treatment with semaglutide at 1mg dose (for diabetes) is between 2 to 3 years, but weight loss is substantially less than with semaglutide 2.4mg (for weight loss)
- SCALE trial provides weak evidence but may not be that helpful for estimating weight regain due to 12 week follow up (weight regain is not linear) and lower overall weight loss

	Semaglutide vs diet and exercise	ICER (£/QALY)
Scenarios based on company base case	**Company base case†**	14,827
	1-year catch up rate*	23,686
	2-year catch up rate*	19,860
Scenarios based on ERG base case	**ERG base case†**	16,337
	1-year catch up rate*	25,746
	2-year catch up rate*	21,060
	4-year catch up rate*	13,501

†Company and ERG base case include 3 year catch up rate

*Catch up rate = time for population treated with semaglutide to reach weight in line with diet and exercise group (not time to return to baseline weight)

NICE

What is an appropriate assumption for time to weight regain?

Retreatment

Royal College of Physicians

- In absence of continued treatment, a rule around restarting treatment should at least be included

British Dietetic Association

- Recommendation around retreatment lacks clarity

Web comments:

- Clarity is needed on when retreatment is an option – would they need to re-meet the recommendation criteria or should a restarting rule be included?
- Given the 2 year maximum treatment duration, comment on retreatment should be made

ACD: Retreatment may be appropriate for some people
Note - no retreatment is assumed in the model

Should a recommendation on retreatment be considered?

Risk equations and estimation of long-term clinical effectiveness (1)

NHS England:

- Inappropriate to use QRISK-3 to predict long-term risk of CVD events when using a time-limited course of semaglutide – weight regain will lead to loss of any potential benefit with surrogate outcomes
- CPRD-GOLD database (6 year median follow-up and including ~49,000 individuals achieving weight loss and ~523,000 individuals with stable weight) shows beneficial impact on surrogate risk factors for CVD not associated with any benefit in hard CV outcomes (atrial fibrillation, heart failure, unstable angina or myocardial infarction)
  - baseline risk for CVD events based on QRISK-3 in CPRD-GOLD population is greater than in STEP 1

ACD: No practical alternative; may be that short term improvement in weight and risk factors provides long term benefit, but no evidence

Abbreviations: CVD – cardiovascular disease; ICER – incremental cost effectiveness ratio

Risk equations and estimation of long-term clinical effectiveness (2)

ERG

- Benefits on CV outcomes may not be detectable even in large studies with limited follow-up
- Haase et al. suggests lower BMI is associated with risk reduction for type 2 diabetes, sleep apnoea and other complications

	Semaglutide vs diet and exercise	ICER (£/QALY)
Scenario based on ERG base case	ERG base case	16,337
	Exclusion of CVD benefits	18,376
	Exclusion of CVD and diabetes benefits	26,668

Suggests benefits associated with diabetes prevention are more influential than CVD event prevention

STEP 1 data shows semaglutide is effective compared with diet and exercise alone for shifting diabetic status from non-diabetic hyperglycaemia to normoglycemic (treatment difference: 59.2%)

NICE

Is the uncertainty around use of risk equations acceptable?

Abbreviations: CV – cardiovascular; ICER – incremental cost effectiveness ratio

Consideration of specific populations (2)

People with severe mental illness (SMI):

- People with SMI are at specific increased risk of metabolic consequences of obesity (RCP)
- Current recommendations may unlawfully discriminate against people with SMI (web comment):
  - Access to tier 3 services for people with SMI is obstructed directly by the referral criteria and indirectly by requirement for high level engagement and previous self-directed efforts at weight loss which are harder for people with SMI – potential equalities issue if only recommended in specialist weight management services (SWMS)
  - SMI medication causes weight gain and metabolic consequences, which leaves people with SMI at elevated risk of most complications of obesity
  - Evidence that diet and lifestyle programmes are not effective for weight loss for people with SMI
  - Liraglutide has shown positive results for weight loss in people with SMI
  - Prevention of comorbidity associated with obesity may be more cost-effective in people with SMI, as this population is more likely to suffer complications, less able to self-manage diabetes and mental illness increases the likelihood of needing institutional care after stroke
  - Semaglutide should be offered to people with SMI via secondary care mental health services (not SWMS)

Abbreviations: SWMS – specialist weight management services

Consideration of specific populations (2)

People with previous bariatric surgery:

- Model not adequate to assess cost effectiveness in this population (web comment):
  - people who have previously had obesity, bariatric surgery, weight loss and then weight regain are not comparable to the health states in the model, which represents people using semaglutide as a relatively early intervention
  - inclusion of downstream bariatric surgery in model does not apply for this group
  - assumptions about monitoring costs are not applicable as already under follow up for surgery
- People with previous bariatric surgery would benefit from long-term maintenance treatment with semaglutide (patient expert)

Diabetes:

- Obesity is the most significant modifiable risk factor associated with diabetes – semaglutide is an important step in mitigating this (web comment)

Other populations:

- Semaglutide could be useful for people with BMI 30 to 34.9 required to lose weight prior to surgery (e.g. gynaecological procedures) or who need to reach BMI <30 to be eligible for IVF (RCP)
- Pregnant women should be prioritised for obesity management (web comment)

Are changes to the recommendations required to consider any specific populations?

Wording of the recommendations

Use of word "exceptionally" regarding recommendation for people with BMI 30 to 34.9 kg/m^2

- Infers only some people with BMI 30 to 34.9 in SWMS are eligible for treatment (company)
- Could result in need for a case by case review via an exceptional case panel (company)
- Is vague and unclear what this means in practice (BDA, web comments)
- Population who are BMI 30 to 34.9 will not be eligible only 'exceptionally' according to the NICE clinical guideline criteria, which is broad (web comments)

"Use lower BMI thresholds (usually reduced by 2.5kg/m^2) for people from south Asian, Chinese, and Black African or Caribbean family backgrounds."

- Should be replaced by a clear threshold (web comment)

"Recommended for people with at least 1 weight-related comorbidity":

- Lack of definition of weight-related comorbidity covers a broad range of comorbidities such as low mood or joint pain (web comments)

Weight-related comorbidity is defined in clinical trial as: hypertension, dyslipidaemia, obstructive sleep apnoea or cardiovascular disease

Are any changes to the recommendation wording appropriate?

NICE

Abbreviations: SWMS – specialist weight management services; BDA: British Dietetic Association

Other comments

- Company and some web comments welcomed recommendation
- Convenience:
  - semaglutide more convenient than liraglutide with once-weekly administration
- Unreasonable to include stopping rule for people who have not lost 5% body weight at 6 months
  - most people achieve >5% weight loss but difficult to estimate treatment length and if weight loss is influenced by delays in accessing treatment
- Unclear when semaglutide would be appropriate compared with bariatric surgery
  - inappropriate to provide both as treatment options as no evidence of these in parallel and not possible to assess surgical readiness properly in conjunction with semaglutide use
  - concerns that people with new onset type 2 diabetes and BMI ≥ 35 will be offered semaglutide rather than referral for bariatric surgery

Key issues following consultation

- Concerns around implementation in tier 3 services associated with tier 3 service distribution across the country – **consideration of treatment setting**
- Inclusion of **2 year stopping rule**
- Uncertainty for **time to regain weight** following discontinuation
- Uncertainty around use of **retreatment**
- Use of **risk equations** for a time limited intervention to predict long term cardiovascular outcomes
- Consideration of **specific populations**:
  - People with severe mental illness (for whom access to tier 3 services is limited)
  - People who have had previous bariatric surgery (different modelling may be required to estimate cost effectiveness in this population)
  - People who may particularly benefit from semaglutide (people who need to lose weight for surgery or to start IVF; people who are planning pregnancy; people with diabetes)
- **Wording of recommendations**:
  - Term ‘exceptionally’ for referral of people with BMI 30 to 34.9 kg/m2
  - Defining weight-related comorbidity in the recommendation
  - Providing a clear BMI threshold for people from south Asian, Chinese, and Black African or Caribbean family backgrounds
- **Stopping rule for people who lose <5% body weight at 6 months**
- **Uncertainty around use compared with bariatric surgery**
- **Are there any uncounted benefits not captured by the QALY calculation?**

Cost effectiveness results

Recap

Cost effectiveness results: liraglutide eligible subgroup

(BMI ≥ 35 kg/m^2 plus pre-diabetes plus high CVD risk)

- Cost-effectiveness estimates based on discounted liraglutide PAS price (available as liraglutide also marketed by Novo Nordisk)

Semaglutide vs liraglutide	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company base case	[redacted]	[redacted]	Dominant
ERG base case	[redacted]	[redacted]	600
Cumulative change from company base case to ERG base case			
+ people with non-diabetic hyperglycaemia do not develop T2D immediately after a CVD event	[redacted]	[redacted]	Dominant
+ mean increase in weight by 0.3 kg per year	[redacted]	[redacted]	Dominant
+ mean decrease in weight after age 66: 0.3 kg per year	[redacted]	[redacted]	Dominant
+ age at which weight no longer decreases: 66 years	[redacted]	[redacted]	Dominant
+annual cost of sleep apnoea	[redacted]	[redacted]	600

Abbreviations – PAS – patient access scheme; T2D: type 2 diabetes; CVD – cardiovascular disease; ICER: incremental cost effectiveness ratio; QALY: quality adjusted life year

Company cost effectiveness results: company target population (BMI ≥ 30 kg/m^2 plus at least 1 comorbidity)

Wider than draft recommendation which restricts access for people with BMI 30 to 35kg/m^2 to those with tier 3 referral based on criteria in CG189

Semaglutide vs diet and exercise	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Scenarios based on company base case			
Company base case (deterministic)	[redacted]	[redacted]	14,827
Company base case (probabilistic)	[redacted]	[redacted]	14,733
1-year catch up rate	[redacted]	[redacted]	23,686
2-year catch up rate	[redacted]	[redacted]	19,860
No stopping rule (for <5% weight loss after 6 months)	[redacted]	[redacted]	19,486
Using STEP 2 data (including T2D population) in model	[redacted]	[redacted]	21,277
Using STEP 2 data in illustrative diabetes model	[redacted]	[redacted]	16,613
T2D incidence: Framingham offspring risk equation	[redacted]	[redacted]	18,337
1st CVD event incidence: Framingham heart study risk equation	[redacted]	[redacted]	13,597
Recurrent CVD event in T2D incidence: Framingham recurring coronary heart disease risk equation	[redacted]	[redacted]	15,154
CVD in T2D incidence: QRisk3 risk equation	[redacted]	[redacted]	13,813

T2D: type 2 diabetes; CVD – cardiovascular disease; ICER: incremental cost effectiveness ratio; QALY: quality adjusted life year

ERG cost effectiveness results – scenario analyses: company target population

(BMI ≥ 30 kg/m^2 plus at least 1 comorbidity)

Wider than draft recommendation which restricts access for people with BMI 30 to 35kg/m^2 to those with tier 3 referral based on criteria in CG189

Semaglutide vs diet and exercise	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Scenarios based on ERG base case			
ERG base case (deterministic)	[redacted]	[redacted]	16,337
Mean starting BMI 32.5	[redacted]	[redacted]	22,192
Mean starting BMI 37.5	[redacted]	[redacted]	14,980
Mean starting BMI 42.5	[redacted]	[redacted]	12,867
1-year catch up rate	[redacted]	[redacted]	25,746
2-year catch up rate	[redacted]	[redacted]	21,060
4-year catch up rate	[redacted]	[redacted]	13,501
Treatment duration: 3 years	[redacted]	[redacted]	17,747
Exclude CVD benefits	[redacted]	[redacted]	18,376
Exclude CVD and diabetes benefits	[redacted]	[redacted]	26,668

NICE

Abbreviations: ICER: incremental cost effectiveness ratio; QALY: quality adjusted life year

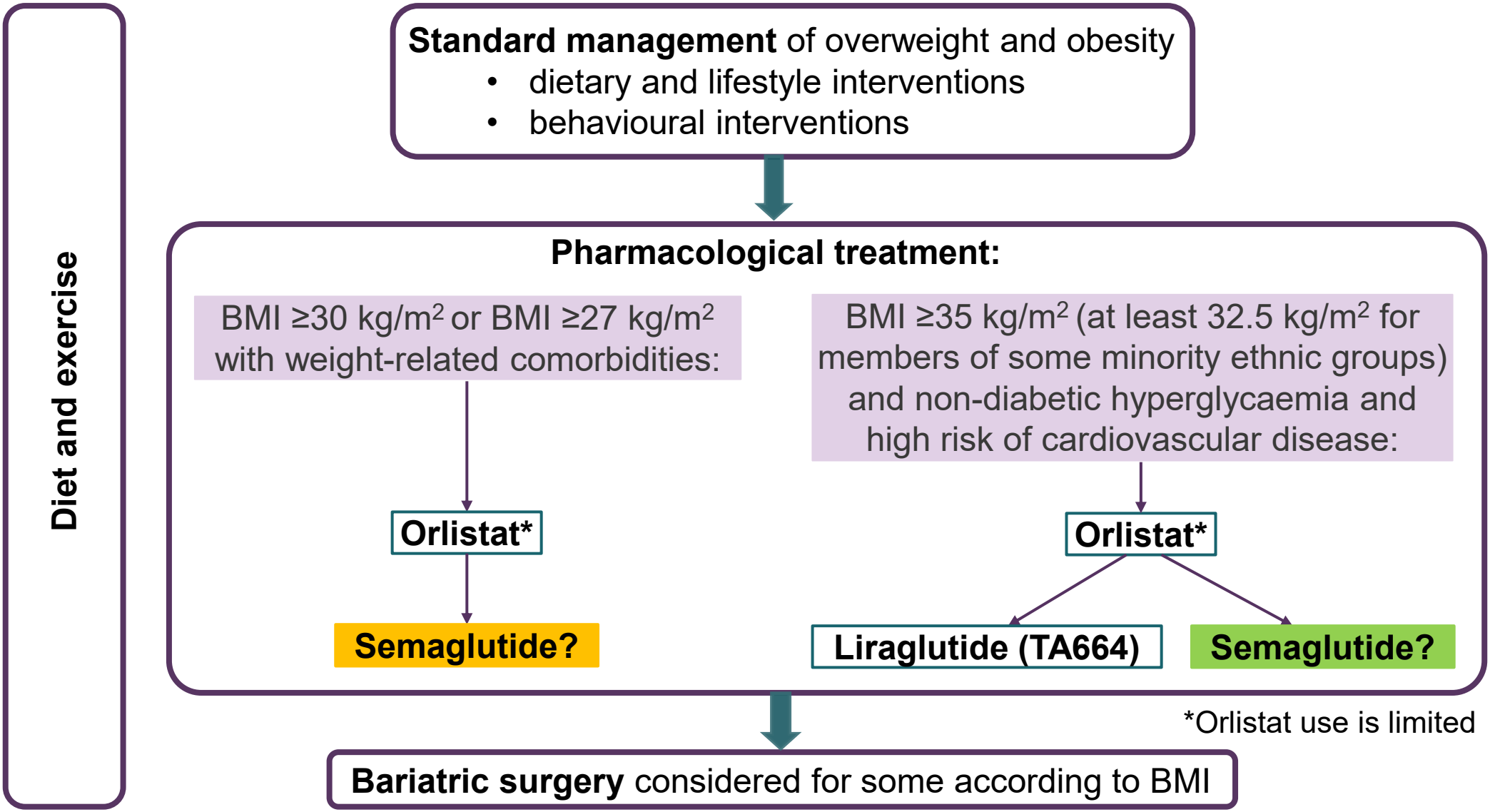
Additional slides for information (not to be presented)

Semaglutide 2.4mg

Marketing authorisation (Received Sept 2021)	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 *Weight related comorbidity not defined in MA. STEP 1 trial specifies: hypertension, dyslipidaemia, obstructive sleep apnoea or cardiovascular disease*
Mechanism of action	Binds to and activates GLP-1 receptors in the brain which regulate appetite and calorie intake; reduces blood glucose by stimulating insulin secretion and lowering glucagon secretion when blood glucose is high
Dose	**Induction dose:** • 0.25 mg, titrated up every 4 weeks (0.5 mg, 1.0 mg, 1.7 mg, 2.4 mg) **Maintenance dose** (after 16 weeks): • 2.4 mg
Administration	Once-weekly by subcutaneous injection, any time of day with or without meals
List price	Solution for injection, packs of 4 pre-filled pens: • 0.25 mg, 0.5 mg, 1 mg dose: £73.25 • 1.7 mg dose: [redacted] • 2.4 mg dose: [redacted]
Other indication	Marketed under a different brand name for control of type 2 diabetes (1 mg dose)

Abbreviations: MA – marketing authorisation; GLP-1 glucagon-like peptide 1

Treatment pathway



The company suggested target population: BMI ≥30 plus a weight related co-morbidity – not **all** currently treated in tier 3 (some people with BMI between 30 to 35 are eligible for tier 3 services in line with NICE clinical guideline recommendations)

NICE

Recommended for some at ACM1

Recommended at ACM1

Recap

Decision problem

	Final scope issued by NICE	Model parameters
Population	People with BMI of: • ≥ 30 kg/m^2 (obese) **or** • ≥ 27 kg/m^2 to < 30 kg/m^2 (overweight) in the presence of at least one weight-related comorbidity	People with BMI of: • ≥30 kg/m^2 and ≥1 weight-related comorbidity • ≥35 kg/m^2 and non-diabetic hyperglycaemia, and high risk of cardiovascular disease
Intervention	Semaglutide 2.4mg	Semaglutide 2.4mg

Comparators	• Standard management without semaglutide
	• Liraglutide for people with:
	  ○ BMI ≥ 35 kg/m^2 and,
	  ○ non-diabetic hyperglycaemia, and,
	  ○ high risk of cardiovascular disease
	• Orlistat (prescription dose)
		For people with:
		• BMI ≥30 kg/m^2 and ≥1 weight-related comorbidity
		Standard management without semaglutide
		
		For people with BMI ≥ 35 kg/m^2 and non-diabetic hyperglycaemia, and high CVD risk:
		• Liraglutide

Outcomes	• BMI • weight loss • waist circumference • incidence of type 2 diabetes • glycaemic status • cardiovascular events • mortality • adverse effects of treatment • health-related quality of life.	• weight loss • glycaemic status • change in systolic blood pressure from baseline • change in fasting lipid profile from baseline (HDL and total cholesterol)

STEP 1: semaglutide compared with placebo

Trial design	Randomised, double-blind, placebo-controlled trial
Population	N= 1,961, 73% female, mean age 46 Adults with obesity alone (BMI ≥ 30 kg/m^2), or overweight (BMI ≥ 27 kg/m^2) with at least 1 weight-related comorbidity (hypertension, dyslipidaemia, obstructive sleep apnoea or cardiovascular disease) and without diabetes **Post hoc analysis of STEP 1 trial:** • People with BMI ≥30 kg/m^2 plus ≥1 comorbidity **(N= 1,470; 75% of ITT)** *(company target population)* • People with BMI ≥35 kg/m^2 plus non-diabetic hyperglycaemia plus high CVD risk subgroup **(N=421; 21.5% of ITT)** *(liraglutide eligible population)*
Intervention	Semaglutide once weekly adjunct to lifestyle intervention (counselling and a reduced calorie diet [500 kcal/day deficit] and 150 mins/week physical activity) 16 week dose escalation increased to maintenance dose of 2.4mg for 52 weeks (68 weeks total treatment)
Primary outcomes	% change in body weight from baseline to 68 weeks Proportion of people achieving baseline body weight loss ≥ 5% at 68 weeks

NICE

Abbreviations: ITT – intention to treat; CVD – cardiovascular disease

ERG cost effectiveness results: company original target population

(BMI ≥ 30 kg/m2 plus at least 1 comorbidity [wider than draft recommendation])

Semaglutide vs diet and exercise	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Cumulative change from company base case to ERG base case			
Company base case	[redacted]	[redacted]	14,827
+ people with non-diabetic hyperglycaemia do not develop T2D immediately after a CVD event	[redacted]	[redacted]	15,336
+ mean increase in weight by 0.3kg per year	[redacted]	[redacted]	13,925
+ mean decrease in weight after age 66: 0.3kg per year	[redacted]	[redacted]	14,393
+ age at which weight no longer decreases: 66 years	[redacted]	[redacted]	14,414
+annual cost of sleep apnoea	[redacted]	[redacted]	16,337
ERG base case	[redacted]	[redacted]	16,337

Abbreviations – T2D: type 2 diabetes; CVD – cardiovascular disease; ICER: incremental cost effectiveness ratio; QALY: quality adjusted life year

Company editorial comments (1)

Company comment	Suggested change to ACD
Term ‘intensive lifestyle interventions’ in ACD not in line with marketing authorisation wording and usually associated with intensive behavioural therapy, not reflective of UK practice	Remove term ‘intensive’.
Target population stated in submission as people with BMI of ≥ 30 mg/kg^2 with ≥1 weight-related comorbidity for patients who are eligible for treatment within SWMS, therefore recommendation is not restricted version of company target population	Statement in submission assumes all people with BMI of ≥ 30 mg/kg2 with ≥1 weight-related comorbidity are eligible for tier 3 services. Based on draft recommendation, population is a restricted version of company’s target population (includes only those eligible for tier 3 services). No change to ACD needed.
Semaglutide use alongside diet and exercise is in marketing authorisation and the main reason it should not be used as stand-alone treatment	ACD describes the marketing authorisation and clinical expert opinion on use as stand-alone treatment. No change to ACD needed.
Query if larger proportion of high-risk population in clinical practice compared with STEP 1 population refers to general clinical practice or SWMS	ACD refers to the general population, not SWMS population. Amend ACD to clarify population.
Clarify population with T2D *and obesity* can be treated in weight-management services	Amend ACD to clarify population.

Abbreviations: ACD – appraisal consultation document

Company editorial comments (2)

Company comment	Suggested change to ACD
Use new bullet in recommendations for BMI criteria for specific ethnicities	No change to ACD needed.
'The assumption that all people develop type 2 diabetes after a CVD event is not correct' is misleading. Only refers to people with non-diabetic hyperglycaemia and alternative approach is also not correct	Clarify wording to note that the model assumes all people with non-diabetic hyperglycaemia develop type 2 diabetes after a CVD event.
Use 'semaglutide 2.4mg' across document to avoid confusion with semaglutide available at other doses	Dosage information is provided in section 2.2. No change to ACD needed.
Liraglutide as comparator should be described as liraglutide *3mg as an adjunct to lifestyle intervention*	Amend ACD as suggested.
Correct sleep apnoea costs in company and ERG's assumptions	Amend ACD as suggested.
Correct average BMI stated for STEP 1	Amend ACD as suggested.

Abbreviations: ACD – appraisal consultation document

Comments raised outside remit of appraisal

- Obesity guideline should emphasise that bariatric surgery is also an option for people with type 2 diabetes and BMI ≥ 35
- Obesity and type 2 diabetes guidelines should cross-refer to this guideline
  - to pass comments onto guideline development team
- Unclear if semaglutide is started in hospital tier 3 setting, if prescriptions could continue in primary care and who would fund this
  - funding cannot be covered in TA
- Support and education needs to be adjusted for people with additional needs
  - implementation issue cannot be covered in TA
- Lack of evidence for GLP-1 analogues in other conditions should be considered
  - populations outside scope of this TA cannot be considered
- No evidence presented that semaglutide use without tier 3 support will not work
  - evidence considered for semaglutide within it's marketing authorisation, which specifies semaglutide alongside diet and exercise (considered assessable in specialist weight management services)

Abbreviations: TA – technology appraisal