National Institute for Health and Care Excellence

Health Technology Evaluation

Orforglipron for managing overweight and obesity ID6516
Response to stakeholder organisation comments on the draft remit and draft scope

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	All About Obesity	Evaluation and proposed evaluation route are acceptable	Comment noted.
	British Obesity and Metabolic Specialist Society	Appropriate	Comment noted.
	Eli Lilly (company)	Yes, this is an appropriate topic to refer to NICE for Single Technology Appraisal	Comment noted.
	Kidney Research UK	No further comment	Comment noted.
	NHS England	STA is appropriate	Comment noted.

Section	Stakeholder	Comments [sic]	Action
	Primary Care Cardiovascular Society	TA is appropriate. Depending on the timing of the clinical trial programmes and licencing there are likely to be other oral medicines for obesity	Thank you for your comments. No change to the scope is required
	Society for Endocrinology	We note that NICE is intending to appraise orforglipron for obesity/overweight. We believe that this medication is important for the following reasons: • obesity is still a highly prevalent, highly comorbid but under-recognized and under-treated condition • obesity management choices are still highly restricted with encumbering criteria applied to the NICE recommendation for Wegovy, and NHSE criteria for Mounjaro. • as a result, very few people are being medically treated for obesity in the NHS and this is increasing health inequalities as only people who can afford private prescriptions are taking pharmacotherapy up. • Orforglipron offers a new choice for obesity treatment which is more suitable for initiation in primary care, as the formulation is oral, and does not require injection training. • It also does not have the restrictions on fasting and timing that are required for oral semaglutide. • The oral formulation is also environmentally less impactful as disposal of plastic injection devices and sharps are not required. The drug does not require a cold chain for distribution, reducing its carbon footprint. • Although somewhat less effective than injectable GLP-1 analogues in terms of weight loss, this magnitude of weight loss is actually ideal for people with BMI <35 where there are identifiable complications of obesity (such as hypertension, hypercholesterolaemia, heart disease, diabetes/pre-diabetes etc.) or where weight loss is required to access treatments such as cancer treatment, surgery, and fertility treatment.	Thank you for your comments. No change required

Section	Stakeholder	Comments [sic]	Action
		Current criteria for access to pharmacotherapies restrict access to BMI >35. Therefore we welcome efforts to provide access for NHS patients to this option for obesity management	
	Renal Pharmacy Group	Appropriate topic	Comment noted
Wording	All About Obesity	Wording is appropriate and reflects the issue of clinical and cost effectiveness about the technologies	Comment noted
	British Obesity and Metabolic Specialist Society	Yes Please avoid using the term obese, instead people living with obesity is better	Thank you for your comment. The wording in the scope has been updated accordingly
	Eli Lilly	Yes, the remit broadly reflects the issue of clinical and cost effectiveness of orforglipron within its marketing authorisation	Comment noted
	Kidney Research UK	No further comment	Comment noted
	NHS England	Appropriate	Comment noted
	Renal Pharmacy Group	Yes	Comment noted
Timing	All About Obesity	Access to weight management medications is very limited, so an increase in options would be beneficial.	Comment noted

Section	Stakeholder	Comments [sic]	Action
	British Obesity and Metabolic Specialist Society	Not urgent	Comment noted
	Eli Lilly	Despite the increasing prevalence of obesity and the substantial humanistic, clinical and economic burden of the condition, the availability of highly efficacious and tolerable treatment options for patients with obesity remains limited in the NHS. A substantial proportion of the population must therefore rely on lifestyle modifications alone to manage their condition, but studies have demonstrated that lifestyle modifications alone are often associated with only modest weight loss and limited clinical benefits. As such, there remains a high unmet need for new clinically effective treatments for managing overweight and obesity, particularly for populations with a BMI ≥27 kg/m^2 with at least one weight-related comorbidity, or BMI 30–35 kg/m^2, where pharmacological therapies are not yet recommended in primary care. Initial results from the ATTAIN-1 (BMI ≥27 kg/m^2 with at least one weight-related comorbidity, or BMI ≥30 kg/m^2 [excluding T2DM]) and ATTAIN-2 trials (BMI ≥30 kg/m^2 with T2DM) demonstrate meaningful reductions in body weight for patients receiving 6 mg, 12 mg or 36 mg oral orforglipron once daily versus placebo over 72 weeks, highlighting the importance of timely evaluation of orforglipron in this indication.	Thank you for your comment. No action required
	Kidney Research UK	Urgent	Thank you for your comment. NICE aims, where possible, to provide timely guidance in line with marketing

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			authorisation. No action needed.
	NHS England	There is likely to be high patient interest/demand so prompt guidance would be helpful	Thank you for your comment
	Primary Care Cardiovascular Society	Given the size of the cohort if an oral agent is available this may free up capacity to allow access for appropriate patients	Thank you for your comment
	Renal Pharmacy Group	Non urgent	Thank you for your comment

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	All About Obesity	Accurate	Thank you for your comment
	British Obesity and Metabolic Specialist Society	Accurate	Thank you for your comment
	Eli Lilly	This section broadly captures the background information of obesity; however, Lilly request the following changes to be made: • Replace “In 2021, 26% of adults in England were obese” with patient-centric language i.e. “In 2021, 26% of adults in England were living with obesity	Thank you for your comment. The scope has been updated accordingly

Section	Consultee/ Commentator	Comments [sic]	Action
		• Remove the sentence “In 2022/2023 there were 8,716 hospital admissions with a primary diagnosis of obesity, a decrease of 22% from a peak of 11,117 admissions in 2018/2019”, as quoting a reduction in hospital admissions implies there has been an improvement in obesity as a public health issue, which is not aligned with published data and epidemiological forecasts.[5,6]	
	Kidney Research UK	Waist to height ratio may be a simpler and more predictive indicator of the early health risks associated with central obesity [Waist-to-height ratio as an indicator of ‘early health risk’: simpler and more predictive than using a ‘matrix’ based on BMI and waist circumference | BMJ Open}] Is chronic kidney disease (CKD) included under the term of weight-related coexisting conditions for this patient population under the CVRM umbrella term? Kidney disease: A UK public health emergency - Kidney Research UK estimates that the current economic burden of kidney disease to the NHS is £7bn a year.	Thank you for your comments. BMI is used in the background section for measuring obesity for consistency with previous scopes. Details about weight-related comorbidities included in the clinical trials have been added to the scope.
	NHS England	Appropriate	Thank you for your comment
	Novo Nordisk	The wording around TA875 should be updated for accuracy and completeness (additional wording added in italics): “NICE TA875 recommends semaglutide as an option for weight management including weight loss and weight maintenance, alongside a reduced-calorie diet and increased activity in adults with at least one weight-related comorbidity and a BMI of at least 35 mg/m2 or a BMI of 30 kg/m2 to 34.9 kg/m2 where the criteria are met for referral to specialist overweight and obesity management services (including but not limited to tiers 3 and 4).”	Thank you for your comment. The scope has been updated accordingly

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	Renal Pharmacy Group	Unclear what the marketing authorisation is as stated in 'The technology' it does not have marketing authorisation but objectives state 'To appraise the clinical and cost effectiveness of orforglipron within its marketing authorisation' Obesity also increases the risk of developing renal disease and progression- suggest adding to the background info	Thank you for your comments. The wording of the proposed marketing authorisation is confidential and cannot be included in the scope. Renal disease has been added to the background section.
Population	All About Obesity	Accurate	Thank you for your comment
	British Obesity and Metabolic Specialist Society	Yes	Thank you for your comment
	Eli Lilly	The population in the draft scope has been defined appropriately	Thank you for your comment
	Kidney Research UK	No further comment	Thank you for your comment
	NHS England	Yes	Thank you for your comment

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	UK Renal Pharmacy Group	As per NICE TAs for tirzepatide and semaglutide does it need to include a lower BMI for certain populations? "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"	Thank you for your comment. The scope has been updated to refer to the lower BMI thresholds that apply to some ethnic minority groups
Subgroups	All About Obesity	Needle phobic People that have been either non-responders to injectable medications or those with extreme adverse effects	Thank you for your comment, no changes to the scope needed
	British Obesity and Metabolic Specialist Society	People with pre-diabetes	Thank you for your comment. If evidence allows, results for relevant subgroups may be considered during the appraisal including subgroups based on BMI and weight-related comorbidities.
	Eli Lilly	There are currently no recommended pharmacological therapies in primary care for patients with a BMI ≥27 kg/m^2 with at least one weight-related comorbidity, or BMI 30–35 kg/m^2, resulting in a notable unmet need for novel and effective therapies in these patients. Orforglipron may therefore be particularly cost-effective for these patients, offering a novel option that may better support these patients to manage their condition.	Thank you for your comment. If evidence allows, results for relevant subgroups may be considered by the committee including subgroups based on

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			BMI and weight-related comorbidities.
	Kidney Research UK	See comments below regarding the inclusion of people from ethnic minority populations and those from socioeconomically deprived backgrounds.	Thank you for your comments
	NHS England	None identified.	Comment noted
	Primary Care Cardiovascular Society	If looking at a lower BMI threshold than the currently NICE approved products would be worth undertaking comparison in different sub-groups as would help define place in treatment pathway Will cardiovascular outcomes also be taken into consideration – as these are likely to be independent to amount of weight loss	Thank you for your comment. If evidence allows, results for relevant subgroups may be considered by the committee during the appraisal including subgroups based on BMI and weight-related comorbidities. Cardiovascular events are included as an outcome in the scope.
	UK Renal Pharmacy Group	CKD patients could potentially be a subgroup, some trials are showing an improvement in renal decline? https://www.nejm.org/doi/full/10.1056/NEJMoa2403347	Thank you for your comment
	All About Obesity	Accurate	Comment noted

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Comparators	British Obesity and Metabolic Specialist Society	Yes	Comment noted
	Eli Lilly	The comparators listed in the draft scope are broadly in line with the standard management options used within current NHS clinical practice to manage overweight and obesity, although the Company suggest that the setting-specific variation for these comparators is also listed in the scope: Primary care: • Diet and exercise • Tirzepatide for BMI ≥40 kg/m2 with ≥3 of the qualifying weight-related comorbidities (atherosclerotic cardiovascular disease [ASCVD], hypertension, dyslipidaemia, obstructive sleep apnoea, or T2DM) for at least the next three years (see discussion of the NHS commissioning policy below) Specialist weight management services (SWMS): • Diet and exercise • Tirzepatide for BMI ≥35 kg/m2 with at least one weight-related comorbidity • Semaglutide for BMI ≥35 kg/m2, or a BMI of 30 kg/m2 to 34.9 kg/m2 (who meet the criteria for referral to SWMS) • Liraglutide for BMI ≥35 mg/kg2 with non-diabetic hyperglycaemia and high cardiovascular risk The Company would also like to note the following points for NICE's consideration: **Relevance of orlistat** Firstly, the Company consider that orlistat should not be considered a relevant comparator in this appraisal. As per the conclusions of the Committee across prior appraisals in obesity and overweight management [TA1026, TA875, TA664, and TA494],7-10 orlistat is not widely used in clinical practice due to its poor efficacy and undesirable side effects. This	Thank you for your comments. These comments have been noted. However at the scoping stage, the list of comparators is inclusive. The company can argue in its evidence submission which comparators are most appropriate to the evaluation for the committee to consider. The typographical error in the scope has been corrected.

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		leads to poor adherence and treatment outcomes, with data published by the National Health Service (NHS) indicating a continued decline in the prescription of orlistat over the last decade.11 Whilst the Company acknowledge that orlistat is recommended in NG246, orlistat should therefore be considered to have a limited role within current UK clinical practice, and thus should not be considered a relevant comparator for orforglipron for the management of overweight and obesity. **Relevance of liraglutide** Liraglutide is only approved for use within a highly restricted population within secondary care. Some patients accessing Tier 3, such as those with a BMI of 30–35 kg/m2 for whom Tier 2 interventions have been unsuccessful, do not even meet the criteria to receive this treatment. In addition, based on indirect treatment comparisons presented in prior appraisals (TA1026, TA875) liraglutide demonstrates inferior efficacy compared with more recently recommended pharmacotherapies, including semaglutide and tirzepatide. As a result, it is understood that uptake of liraglutide in NHS clinical practice is low. The lack of relevance of liraglutide for the broader population with obesity in primary care was reflected in Committee discussions in TA1026, where the Committee agreed that liraglutide is not an appropriate comparator for tirzepatide. **Relevance of semaglutide** The Company also consider that semaglutide should not be considered a relevant comparator in this appraisal. Semaglutide is only approved for use in b (who meet the criteria for referral to SWMS) in the presence of at least one weight-related comorbidity, under the condition it is used for a maximum of 2 years within a SWMS providing multidisciplinary management of overweight and obesity. As highlighted by patient and clinical experts in TA1026, access to SWMS in the UK is limited, particularly for those with a BMI of 30 to 34.9 kg/m2. The Committee therefore concluded in TA1026 that semaglutide did not constitute a relevant comparator to tirzepatide.10 **Description of diet and exercise comparator**	

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		In addition, it is important to highlight that many patients in primary care – where orforglipron is expected to be primarily delivered – simply receive advice on healthy eating and physical activity, rather than receiving recommendations for specific calorie reductions or increases in physical activity. It is therefore recommended that the comparator scope wording is broadened to “standard management without orforglipron (including healthy diet and physical activity)” to better reflect established clinical management for patients with obesity UK primary care. **Availability of tirzepatide** Tirzepatide, alongside a reduced-calorie diet and increased physical activity, has also recently been recommended by NICE in adults, in primary care or secondary care, with a BMI ≥35.0 kg/m2, with at least one weight-related comorbidity. However, it should be noted that following this recommendation, NHS England submitted a funding variation request, on behalf of NHS providers and ICBs, to extend the time needed to comply with the recommendations. The funding variation stipulates that ICBs have a maximum period of 12 years to comply with its introduction, extended from the standard 3 months. As such, under the NHS commissioning policy, tirzepatide is only available for a limited number of people in primary care within the first three years: • Cohort 1 (2025/2026 – Year 1): adults with a BMI ≥40 kg/m2, with ≥4 comorbidities such as, hypertension, dyslipidaemia, obstructive sleep apnoea, cardiovascular disease, and T2DM • Cohort 2 (2026/2027 – Year 2): adults with a BMI ≥35 to 39.9 kg/m2, with ≥4 comorbidities such as, hypertension, dyslipidaemia, obstructive sleep apnoea, cardiovascular disease, and T2DM • Cohort 3 (2026 and 2027/28 – Year 2/3): adults with a BMI ≥40 kg/m2, with ≥3 comorbidities such as, hypertension, dyslipidaemia, obstructive sleep apnoea, cardiovascular disease, and T2DM Consequently, tirzepatide is not established NHS practice in England for all populations for whom it was recommended by NICE and is therefore not an	

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		appropriate comparator to orforglipron outside of the populations defined in the commissioning policy. **Typographical error** Finally, it should also be noted that the comparator scope includes a typographical error when referring to orforglipron.	
	Kidney Research UK	Yes	Comment noted
	NHS England	For the subgroup being treated to prevent the onset of type 2 diabetes, two additional interventions should be considered as comparators: - Metformin (public health guideline 38) - NHS Diabetes Prevention Programme For the subgroup with high BMI, bariatric surgery would be an appropriate comparator (but not for people with a lower BMI). The definition of those suitable for bariatric surgery should reflect NHS practice.	Thank you for your comments. Diabetes specific treatment options have not been included in the scope. Bariatric surgery is only available for a minority of people at higher BMI thresholds and has not been included as a comparator.
	Primary Care Cardiovascular Society	The comparators listed are currently the standard treatments. Depending on the timing of the clinical trial programmes and licencing there are likely to be other oral medicines for obesity. This may affect whether evaluate any of these also as a comparator. The most likely is oral semaglutide.	Thank you for your comment. No change to the scope is required
	UK Renal Pharmacy Group	Would not consider orlistat a comparator. Orlistat was not a comparator for the injectable GLPs. Is bariatric surgery a comparator?	Comment noted. At the scoping stage, the list of comparators is inclusive. Orlistat is a

Section	Consultee/ Commentator	Comments [sic]	Action
			treatment option in CG246 and is included in the scope for completeness. Bariatric surgery is only available for a minority of people at higher BMI thresholds and has not been included.
Outcomes	All About Obesity	Accurate	Comment noted
	British Obesity and Metabolic Specialist Society	Appropriate	Comment noted
	Eli Lilly	The outcome measures presented broadly capture the most important health-related benefits of orforglipron.	Comment noted
	Kidney research UK	Please amend as follows: • Include kidney function tests (eGFR or uACR) as an outcome measure • Amend last bullet point to 'health-related quality of life, including delaying the onset of CKD.' **See [**The Broader Effects of Delayed Progression to End-Stage Kidney Disease: Delaying the Inevitable or a Meaningful Change? - PubMed**].**It would also be useful to use the eGFR and uACR results to calculate the risk of kidney failure (2- and 5-year probability of treated kidney failure for a potential patient with CKD stage 3a to 5) to help understand when to treat	Thank you for your comments. The scope has been updated to include kidney function as an outcome measure.

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		patients with appropriate medication and when to refer patients to renal specialists. See [**The Kidney Failure Risk Equation]**	
	NHS England	Yes	Comment noted
	Renal Pharmacy Group	Appropriate outcomes	Comment noted
Equality	All About Obesity	Accurate	Comment noted
	British Obesity and Metabolic Specialist Society	This is ok	Comment noted
	Eli Lilly	**BMI variations between different ethnicities:** Cardiometabolic risk occurs at a lower BMI for people from South Asian, Chinese, other Asian, Middle Eastern, Black African or African-Caribbean family backgrounds. Ethnicity-specific BMI thresholds recommended by NICE provide a pragmatic approach to defining overweight and obesity in these populations, typically reducing the obesity cut-off by about 2.5 kg/m^2 (from 30 kg/m^2 to 27.5 kg/m^2) to enable earlier detection and intervention in these populations. **Access inequalities for treatment for other disabilities/conditions:** Individuals with overweight or obesity who also have disabilities often face significant barriers to accessing treatments or surgical interventions for their other health conditions. A study assessing commissioners' policies for BMI and smoking status and implications for integrated care systems (ICSs), it was estimated that 61.1% of CCGs with BMI policies introduced extra waiting time before surgery or restricted access to surgery based on BMI thresholds (modal threshold: BMI of 40 kg/m^2, range 30–45). As a result, patients with	Thank you for your comment. These equalities considerations are formally addressed in the Equalities Impact Assessment form.

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		higher BMIs may face prolonged delays before elective surgery while attempting to lose weight in order to meet eligibility criteria. **Socioeconomic inequalities:** People living in deprived areas often face significant barriers to accessing affordable, healthy food and to regularly exercising, contributing to a higher prevalence of overweight and obesity among those with lower socioeconomic status. Data published by the Office for Health Improvement and Disparities for 2023/24 demonstrate that the prevalence of excess weight is 12% higher in the most deprived areas than in the least deprived areas.	
	NHS England	No changes to the scope suggested	Comment noted
Other considerations	All About Obesity	Implementation process	Comment noted. Issues related to implementation regarding access to services cannot be addressed directly in a technology appraisal.
	British Obesity and Metabolic Specialist Society	None	Comment noted
	NHS England	None	Comment noted
	Eli Lilly	None	Comment noted

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	Primary care cardiovascular society	To enable implementation should look for this to be prescribed in general practice or in services commissioned to support general practice and based in the community	Thank you for your comment. Issues related to implementation regarding access to services cannot be addressed in a technology appraisal.
Questions for consultation	British Obesity and Metabolic Specialist Society	**Which treatments are considered to be established clinical practice in the NHS for overweight and obesity?** The ones listed as comparators **Is bariatric surgery a relevant comparator for adults with a BMI of ≥30 kg/m² or adults with a BMI ≥27 kg/m² to <30 kg/m2 and at least one weight-related comorbidity?** Not really as the indications for surgery are different and start at a higher BMI **Are there any subgroups of people in whom orforglipron is expected to be more clinically effective and cost effective or other groups that should be examined separately**? People with pre-diabetes **Where do you consider orforglipron will fit into the existing care pathway for managing overweight and obesity?**	Thank you for your comments. Bariatric surgery is only available for a minority of people at higher BMI thresholds and has not been included.

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		As part of standard of care for people with obesity, alongside existing medications **Please select from the following, will orforglipron be:** A. Prescribed in primary care with routine follow-up in primary care B. Prescribed in secondary care with routine follow-up in primary care C. Prescribed in secondary care with routine follow-up in secondary care D. Other (please give details): A. Would orforglipron be a candidate for managed access? No Do you consider that the use of orforglipron can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? No Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits. Published RCTs for use in people with obesity Please indicate if any of the treatments in the scope are used in NHS practice differently than advised in their Summary of Product Characteristics. For example, if the dose or dosing schedule for a treatment is different in clinical practice. If so, please indicate the reasons for different usage of the treatment(s) in NHS practice. If stakeholders consider this a relevant issue,	

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		please provide references for data on the efficacy of any treatments in the pathway used differently than advised in the Summary of Product Characteristics. No NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope: • could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which orforglipron will be licensed; • could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please tell us what evidence should be obtained to enable the committee to identify and consider such impacts. No	
	Eli Lilly	**1. Which treatments are considered to be established clinical practice in the NHS for overweight and obesity?** Despite the increasing prevalence of obesity in the UK, there are still few effective and tolerable treatment options available for the anticipated population of relevance to this appraisal. There remains a substantial proportion of people with obesity for whom no pharmacotherapies are	Thank you for your comments. At the scoping stage, the list of comparators is inclusive. However the company can argue

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		currently recommended in primary care, such as those with a BMI ≥27 kg/m2 with at least one weight-related comorbidity, or a BMI of 30–35 kg/m2. Discussion of each of the comparators listed in the draft scope is provided below. **Orlistat** As described above, orlistat is available to patients with a BMI ≥30 kg/m^2, or a BMI ≥28 kg/m^2 with other weight-related comorbidities. However, orlistat is associated with undesirable side effects, insufficient weight loss and poor adherence, which means it is now rarely used in UK clinical practice **Liraglutide** Liraglutide is approved for use within a highly restricted population in secondary care and has lower efficacy compared with other more recently recommended obesity medications, limiting its utility in clinical practice. Liraglutide is therefore not a relevant comparator in the primary care setting, where orforglipron is anticipated to be primarily delivered. **Semaglutide** Similarly to liraglutide, use of semaglutide is restricted to SWMS. However, access to SWMS in the UK is limited, and therefore use of semaglutide in patients with a BMI of 30–35 kg/m^2 is extremely limited. As a result, semaglutide is not anticipated to be a relevant comparator to orforglipron. **Tirzepatide** As discussed above, tirzepatide will only be available in SWMS for BMI ≥35.0 kg/m^2 with at least one weight-related comorbidity or in primary care for patients with BMI ≥40 kg/m^2 with ≥3 qualifying comorbidities for at least the next three years per the NHS commissioning policy. As such, tirzepatide does not and will not constitute established clinical practice for at least the next three years for patients in primary care not meeting the criteria defined in the NHS commissioning policy. **Diet and exercise** Given the limited proportion of patients current able to benefit from available recommended pharmacotherapy, diet and exercise remains the sole	in its evidence submission which comparators are most appropriate to the evaluation for the committee to consider.

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		treatment option for many patients with obesity. Clinical trials have consistently demonstrated a limited magnitude of benefit for patients receiving diet and exercise support alone, and this is further supported by real-world evidence which demonstrates that lifestyle interventions alone are not enough to help patients lose weight and maintain weight loss. As such, there remains an important unmet need for novel treatment options that support greater weight loss in patients who would otherwise have to rely on diet and exercise alone to manage their chronic condition. **2. Is bariatric surgery a relevant comparator for adults with a BMI of ≥30 kg/m² or adults with a BMI ≥27?** In England, bariatric surgery is available for patients with a BMI ≥40 kg/m^2, or between 35–40 kg/m^2 and other significant disease accessing SWMS. However, previous appraisals in this indication (TA1026, TA875, TA494, and TA664) have highlighted that bariatric surgery is rarely used in clinical practice, with only around 0.1% of eligible patients actually receiving this treatment. More recent data (2020) suggests that this figure is even lower, at around 0.002%. Furthermore, a freedom of information mapping exercise conducted in 2025 across the 42 ICSs in England, revealed significant disparities in access to bariatric care. Notably, large regions, particularly in the East of England, lack bariatric units, thus limiting access to necessary services. Additionally, 31% of ICSs impose more restrictive criteria for accessing bariatric surgery, which is inconsistent with NICE guidelines and established evidence-based practices. As such, it is not realistic that bariatric surgery would be considered part of established clinical management for the populations of relevance to this appraisal, and subsequently, it should not be considered a relevant comparator for orforglipron. Nevertheless, to account for the fact that bariatric surgery is available for some patients in England as part of SWMS, it is anticipated that bariatric	

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		surgery will be included in the economic model as a downstream event, as per the approach taken in TA1026 **3. Are there any subgroups of people in whom orforglipron is expected to be more clinically effective and cost effective or other groups that should be examined separately?** As outlined earlier, there is a marked unmet need among adults with a BMI ≥27 with weight-related comorbidities, or a BMI of 30–35 kg/m², primarily due to the absence of recommended pharmacological treatments for this group in primary care. As a result, this population is predominantly reliant on lifestyle interventions, such as diet and exercise, which frequently do not yield substantial or sustained weight reduction results. Orforglipron could therefore demonstrate greater cost-effectiveness in these patients by addressing this important unmet need. **4. Where do you consider orforglipron will fit into the existing care pathway for managing overweight and obesity?** • Orforglipron may particularly benefit patients in whom other pharmacotherapies are not yet recommended, given the particularly pronounced unmet need in these patients and the substantial benefits that more marked weight loss may offer these patients compared with lifestyle interventions alone. Given this, and provided the economic evidence allows, orforglipron might be best positioned in primary care for patients with a BMI ≥27 kg/m^2 with at least one weight-related comorbidity, or with a BMI 30–35 kg/m^2 **5. For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention** It is anticipated that orforglipron will be primarily "(A) prescribed within primary care settings with routine follow-up in primary care". However, to ensure broader and equitable access, it is essential that orforglipron is also made available within all other settings that are responsible for	Thank you for your comments. Where evidence allows, results for relevant subgroups may be considered by the committee including subgroups based on BMI and weight-related comorbidities. Thank you for your comments.

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		managing patients with obesity, including secondary care settings. This approach will ensure that patients across different healthcare settings can benefit from orforglipron, without facing unnecessary access restrictions. In December 2024, tirzepatide was similarly recommended for use across both primary and secondary care settings, following the unanimous view of patient experts, clinicians and NHS England that such therapies should not be restricted to SWMS. As such, this should be the default approach for new obesity and overweight management therapies going forwards **6. Would orforglipron be a candidate for managed access?** No **7. Do you consider that the use of orforglipron can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** • Long-term benefits of weight loss extend beyond the health-related benefits captured in the QALY calculation. Peer-reviewed published literature suggests that weight reduction is associated with lower risks of several obesity-related cancers, which are not anticipated to be explicitly captured in the model for this appraisal, including colorectal, liver, gallbladder, kidney, and pancreatic cancers; postmenopausal breast cancer, ovarian cancer, thyroid cancer, endometrial cancer, multiple myeloma, meningioma, and adenocarcinoma of the oesophagus and gastric cardia. Similarly, there are various other comorbidities which demonstrate improvement following weight loss, but which are not anticipated to be explicitly modelled, including (but not limited to) depression and polycystic ovary syndrome. • Beyond direct effects on comorbidity burden, orforglipron could also yield downstream benefits to patients and society. Obesity is one of the biggest drivers of ill health in the UK, placing significant strain on	

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		the NHS, and the wider economy. Wider access to anti-obesity drugs, such as orforglipron, could lead to substantial long-term cost savings; a recent macromodelling study conducted by the Tony Blair Institute for Global Change, suggested that expansion of anti-obesity medications could lead to cumulative fiscal benefits of £52 billion by 2025 in the UK. • Alongside reductions in direct healthcare costs as a result of obesity-related ill heath, weight loss may improve patient independence by supporting return to work or reducing presenteeism, and by enabling participation in daily activities, sport and hobbies, thereby also helping to reduce the indirect costs associated with obesity. Orforglipron could also reduce the clinical and economic burden of postponed or cancelled elective surgeries due to obesity and the higher operative risks when obesity is present	
	Kidney research UK	**Subgroups of people to be considered** People living with chronic kidney disease (CKD) are an under-served and under-recognised patient population in the UK. Growing numbers of people are at risk of kidney disease due to increased cases of diabetes, heart disease, high blood pressure and obesity. [Kidney disease: A UK public health emergency 2023 Economics-of-Kidney-Disease-summary-report_accessible.pdf] Delaying the onset of CKD would be particularly beneficial for 'at risk' populations, such as those who are from ethnic minority groups or socioeconomically deprived. There is evidence that patients with CKD who are socioeconomically deprived have faster disease progression, higher risk of cardiovascular disease and premature mortality. [Deprivation and chronic kidney disease-a review of the evidence – PubMed].	Thank you for your comments. Where evidence allows, subgroups based on weight-related comorbidities may be considered. Thank you for your comments. Equalities considerations will be addressed in the Equalities Impact Assessment form.

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		This patient population often has higher rates of obesity, CVD and CKD but may face greater barriers to accessing new treatments. Lifestyle interventions and follow-up support (e.g. dieticians, exercise programmes) are not always equitably available, especially in deprived areas. With more conditions considering GLP-1s as an earlier line of treatment, the populations most likely to benefit from an oral alternative should be carefully considered. Patients who are socioeconomically deprived may not have access to a fridge and may struggle with keeping an injectable treatment at the correct temperature. **Fitting into existing care pathways** Orforglipron would fit into the existing care pathways at the same point as semaglutide. Current T2D guidelines being developed suggest these lines of treatmetn should be brought forward. See [Biggest shake-up in type 2 diabetes care in a decade announced | NICE]. **Potential health related benefits unlikely to be included in QALY calculation** As noted above, patients treated with orforglipron should benefit from improved kidney function (reflected in eGFR and uACR). See [Variation in the Commissioning of Semaglutide for the Treatment of Obesity and Overweight Across England: Results of Three Freedom of Information-Based Mapping Exercises Across the 42 Integrated Care Boards of England - Bray - Clinical Obesity - Wiley Online Library]. **Equality of opportunity**	

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		In addition to the points raised above, we note there is a disparity in access to GLP-1s in general with those who can afford to pay gaining access to this treatment. See [Are weight-loss treatments contributing to health inequalities? - The Health Policy Partnership].	
	NHS England	Orforglipron is an oral non polypeptide GLP-1 analogue. Given this, it is easier to administer than oral semaglutide (Rybelsus), already commonly prescribed in primary care in the NHS in England. Therefore, given that use of oral GLP-1 therapies is already established in primary care, and that orforglipron is easy to take, without restrictions around eating or other therapies, it seems appropriate that **setting of care should be across care settings.** Thus, orforglipron could be prescribed in primary care with routine follow-up in primary care, and also used in specialist settings. While the majority of Integrated Care Boards (ICBs) have now developed plans for commissioning weight management services, these pathways are at varying stages of development and maturity. Consequently, the availability and readiness of pathways to support the delivery of orforglipron will differ across ICB footprints. This represents a notable distinction from the implementation of NICE guidance for semaglutide (Wegovy®) [TA875] and tirzepatide (Mounjaro®) [TA1026] where, at the time of the appraisals, there were no weight management services available outside of Specialist Weight Management Services (SWMS). An oral therapy offers some benefits over injectables that may not be captured in cost-effectiveness calculations: - No injection site reactions - Environmental benefits (single-use plastic, cold chain storage, transport, sharps, sharps and plastic waste disposal etc)	Thank you for your comments

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	Novo Nordisk	**Is bariatric surgery a relevant comparator for adults with a BMI of ≥30 kg/m² or ≥27 kg/m² to <30 kg/m2 and at least one weight-related comorbidity?** Bariatric surgery is only available to a small number of patients with obesity with a high BMI (a BMI of 40 kg/m2 or more, or between 35 kg/m2 and 40 kg/m2 and other significant disease) and is considered a last resort option. It is therefore not a relevant comparator for this appraisal	Thank you for your comments
	Royal College of Physicians	**Which treatments are considered to be established clinical practice in the NHS for overweight and obesity?** This would depend on how 'established' is defined. For the purposes of this response we would define established as 'an intervention *used in routine practice* across a population, delivered by a healthcare professional with the relevant experience and skillset in that specific intervention, with known outcomes' In line with that definition: • National NHSE programmes such as the Digital Weight Management Programme, Diabetes Prevention Programme and Path To Remission = established. • Medical therapies – orlistat in primary care settings = established. • Bariatric surgery = established treatment in the NHS for overweight and obesity. However, there is variable access and long waiting times. • Gastric bands and balloons = no longer established and good evidence of inferior outcomes compared to bariatric surgery. Also now have a limited role given medical therapies. • Endoscopic sleeve = not established. GLP-1 medications such as Saxenda	Thank you for your comments.

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		(liraglutide), Wegovy (semaglutide) and Mounjaro (tirzepatide) are prescribed in pockets of the country. However, our experts are not convinced that this is established through Specialist Weight Management Service (SWMS) according to NICE guidelines for the reasons below: • Saxenda (liraglutide): since the National Patient Safety Alert, most SWMS are not initiating new patients on Saxenda therefore there is limited experience. • Wegovy (semaglutide): access to SWMS is variable with significant waiting times and restrictions in many ICBs about inclusion criteria. This is because the vast majority of SWMS cannot meet the demand as set out by TA 875. Mounjaro (tirzepatide): Similarly, a significant proportion of SWMS are unable to provide tirzepatide according to TA1026 for the same reasons due to lack of workforce, significant demand and lack of resources to deliver this. Unfortunately, for most SWMS, medical therapies such as semaglutide and tirzepatide are not established clinical practice because there is limited experience in the cohorts and numbers of patients receiving this in SWMS compared to the population living with obesity. **Q. Is bariatric surgery a relevant comparator for adults with a BMI of ≥30 kg/m² or adults with a BMI ≥27 kg/m² to <30 kg/m² and at least one weight-related comorbidity?** Our experts note that the criteria for bariatric surgery on the NHS is a BMI 35-40 kg/m² with at least one weight related co-morbidity or a BMI ≥40 kg/m², and as such it would not be a relevant comparator for adults with a BMI of ≥30 kg/m² or adults with a BMI ≥27 kg/m² to <30 kg/m2 and at least one weight related comorbidity. However, bariatric surgery is performed on patients with BMI >35 and one weight-related co-morbidity, with significantly better outcomes than	

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		orforglipron. It is important therefore to compare new treatments against all available therapies. This would include medical therapy comparators such as liraglutide (Saxenda), semaglutide (Wegovy) and tirzepatide (Mounjaro). NICE may also wish to include orlistat as an oral preparation comparator. If excluding bariatric surgery on the grounds of different BMI threshold, then the same would apply to liraglutide, semaglutide and tirzepatide and therefore orlistat would be your only comparator. The exception here would be if you compared against licenced criteria according to the MHRA which is different to NICE guidance. **Q. Are there any subgroups of people in whom orforglipron is expected to be more clinically effective and cost effective or other groups that should be examined separately?** Our experts are not aware that the information to answer this question is available from the clinical trials published to date. Based on NEJM publication from the GZGI Investigators (Wharton et al, phase 2 clinical trial), 90% of participants were white ethnicity which has obvious implications for rolling out on a national scale. More recently the phase 3 clinical trial was published by the same group however patients with type 2 diabetes were excluded. Mean body weight loss was 7.5 – 11.2% depending on the dose. In the clinical trials published so far by the same group, the co-morbidities specified were hypertension, dyslipidaemia, cardiovascular disease and obstructive sleep apnoea. We would therefore recommend looking at these subgroups, in the absence of other available data. More recent publications have looked at the role of orforglipron in Type 2 diabetes so this is one cohort that needs to be looked at. However, we know from most clinical trials that patients with T2DM with higher HbA1c, that they lose less weight in response to GLP-1 receptor agonists compared to patients	

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		without diabetes. However the comparator here would be oral semaglutide for patients with T2DM and perhaps focusing on whether there is benefit in the use of orforglipron for weight loss in patients with T2DM but below a certain HbA1c threshold (higher HbA1c would likely benefit more from semaglutide s/c or tirzepatide). We would also hope that SMI (severe mental illness) would be factored in the consultation as a group warranting specific consideration. **Q. Where do you consider orforglipron will fit into the existing care pathway for managing overweight and obesity?** In the absence of head-to-head clinical evidence, it is difficult to know where orforglipron would fit but our experts would suggest: • Treatment failure (according to HbA1c) with oral semaglutide for patients with T2DM (this would sit in diabetes guidelines though rather than in an obesity guideline) • Consider for weight loss in T2DM below certain HbA1c threshold (see above) • Weight maintenance after successful weight loss ('successful' to be defined) after subcutaneous semaglutide or tirzepatide. There is currently no evidence to support this and therefore could be a suggested area for research. • Lower BMI with required weight loss of around 10% (see below) In terms of where these medical therapies fit alongside each other and bariatric surgery, it would be very helpful to focus on the primary indication for weight loss and the amount of weight loss required to 'reverse' that particular condition. The EASO has some helpful definitions and our experts would support this stance. Therefore, orforglipron could sit in a place whereby the	

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		required weight loss would equate to around 10% and is largely dependent on their starting BMI. There is questionable rationale in starting patients on certain medical therapies if their BMI is above 50. While there might be benefits for <u>any</u> weight loss, the likely health and economic benefits will be realised and more advantageous if the primary indication for weight loss is reversed. For example, if the required weight loss outcomes are: • <10% - diet and exercise intervention e.g. national weight loss programmes, orlistat, orforglipron • 10-15% - s/c semaglutide • 15-25% - tirzepatide • >25% - bariatric surgery The two areas where this might differ would be in patients with cardiovascular disease (semaglutide and should sit in CVD guideline), chronic kidney disease and T2DM (semaglutide and this should sit in diabetes and renal guidelines). Treatment failure or continued side effects at any stage could mean going up to the 'next level' i.e. similar approach to hypertension treatment is required however I would strongly recommend bariatric surgery for patients with a BMI over 50 and multiple comorbidities, alternatively tirzepatide. In terms of existing care pathways – all medical therapies should be available in primary and secondary care settings, leaving bariatric surgery to SWMS/Tier 4 services. It is then up to ICBs to determine how the pathways and shared care agreements (where applicable) should be applied. Finally, it might be worth trying to do sub analysis or call for research into the role of orforglipron in prevention of obesity. Given that weight loss outcomes are around 10% - perhaps there is a role for patients with BMI 25-30 as this is	

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		a 'missed' group for the majority of weight loss interventions and could sit well alongside diet and exercise/digital/Tier 2 services. This might be particularly relevant in patients under the age of 40 (as per T2DM subgroup analysis and recommendations). **Q. Please select from the following, will orforglipron be:** **A. Prescribed in primary care with routine follow-up in primary care** **B. Prescribed in secondary care with routine follow-up in primary care** **C. Prescribed in secondary care with routine follow-up in secondary care** **D. Other (please give details)** Our experts support prescribing in line with B. but also extended to D. where prescribing would occur in both primary and secondary care. Medical therapies for weight loss should not be restricted depending on whether patient is seen in primary or secondary care. **Q. For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention.** Patients could be assessed by specialist weight management clinics and established on orforglipron and then handed back to primary care to continue treatment. This would ensure more patients have access to the treatment and it is only continued if adequate weight loss is achieved. Patients will also have consistent support and advice to manage side effects. **Q. Would orforglipron be a candidate for managed access?** Potentially yes, as that would allow collection of real-world efficacy data and highlight any regional variations in prescribing/availability. Our experts would	

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		defer this decision to NHSE and NICE to consider whether this would be appropriate. **Q. Do you consider that the use of orforglipron can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** Potentially in weight maintenance, although this lacks evidence and therefore unknown but could be helpful information when doing modelling. **Q. Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits**. See above.	
	Renal Pharmacy Group	**Where do you consider orforglipron will fit into the existing care pathway for managing overweight and obesity?** Similar to tirzepatide- can be initiated and continued in primary care And in secondary care as part of a weight loss service	Comments noted

The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope:

Neonatal and Paediatric Pharmacists Group