National Institute for Health and Clinical Excellence

Single Technology Appraisal (STA)

Phentermine with topiramate for the treatment of obesity and overweight

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	Arena Pharmaceuticals	NICE clinical guideline 43 for the prevention, identification, assessment and management of overweight and obesity in adults and children recommends that drug therapy be considered after dietary, exercise and behavioural approaches have been started and evaluated. Currently the only available therapy is Orlistat, which is associated with certain gastrointestinal side effects. As additional therapies are needed for physicians to treat obesity, it is appropriate to refer this topic to NICE for appraisal.	Comment noted. No change to the scope required.
	NHS Warwickshire	The topic is appropriate given the growing burden of obesity on population health and healthcare cost. Currently, the only medication recommended as an adjunct for the promotion of weight loss is Orlistat, which reduces the absorption of fat in the gastrointestinal tract. Phentermine is a centrally acting appetite suppressant and topiramate has weight loss properties. We understand that this medication, as per NICE clinical guidelines, will only be considered for use after dietary, exercise and behavioural approaches have been started and properly evaluated. It is hoped that a NICE appraisal will offer an independent review of the comparative clinical- and cost-effectiveness of phentermine with topiramate for the treatment of obesity and overweight relative to orlistat.	Comment noted. Consultees at the scoping workshop agreed that orlistat (both low and high dose preparations) was the most appropriate comparator for an appraisal of phentermine.
	VIVUS BV	We support referral of the topic to NICE. No further comments.	Comment noted. No change to the scope required.

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Wording	Arena Pharmaceuticals	Yes	Comment noted. No change to the scope required.
	NHS Warwickshire	The wording seems appropriate.	Comment noted. No change to the scope required.
Timing Issues	NHS Warwickshire	The appraisal should take long enough to assess the clinical endpoints. However, given that phentermine with topiramate does not yet have a UK marketing authorisation for the treatment of obesity and overweight, we would suggest that it is most helpful if it is issued as close as possible to the granting of a marketing authorisation.	Comment noted. An appraisal will be scheduled with the aim of guidance being issued within 6 months of the marketing authorisation being granted.
	VIVUS BV	With overweight and obesity effecting two thirds of adults in England and Wales, we believe there is an urgent public health need for timely appraisal of this new medicinal product for use in England and Wales.	Comment noted. An appraisal will be scheduled with the aim of guidance being issued within 6 months of the marketing authorisation being granted.
Additional comments on the draft remit	VIVUS BV	The current appraisal objective is based on the proposed indication as submitted with the initial application, and may change based on the CHMP final opinion.	Comment noted. Recommendations will only be made in line with the final marketing authorisation.

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	Arena Pharmaceuticals	It appears complete.	Comment noted. No change to the scope required.

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	NHS Warwickshire	No comments on cost and side effects of this combination drug have been given.	Comment noted. No change to the scope required.
	VIVUS BV	Appropriate.	Comment noted. No change to the scope required.
The technology/ intervention	Arena Pharmaceuticals	Yes.	Comment noted. No change to the scope required.
	NHS Warwickshire	Use of the medication together with behaviour modification is most appropriate. Phentermine with topiramate has no marketing authorisation in the UK. An independent review of the stated clinical trials is essential.	Comment noted. An appraisal will be scheduled with the aim of guidance being issued within 6 months of the marketing authorisation being granted.
	VIVUS BV	The brand name is Qsiva, and one of the components of the product is a controlled-release topiramate. Topiramate has documented weight loss activity, as well as metabolic (glycemic and lipid) and blood pressure lowering effects. Qsiva has been studied in clinical trials for up to two years. Would consider modifying the language to "behavioural modification and a weight-reducing diet". Otherwise the description wording is accurate.	Comment noted. At the scoping workshop consultees agreed that behavioural modification often includes a weight-reducing diet and therefore no changes to the wording of the technology section in the scope are required.
Population	Arena Pharmaceuticals	The population names should include a method of identification, such as BMI: Obese adults (BMI ≥ 30 kg/m^2) Overweight adults (BMI > 27 kg/m^2) with weight-related comorbid conditions. Phentermine with topiramate in unlikely to be recommended for use in women of child-bearing potential (since topiramate is a teratogen); hence, it may be appropriate to consider a population of obese and overweight adults that excludes women of childbearing potential.	Comment noted. Consultees discussed if BMI ranges should be used to differentiate between obese and overweight populations. Consultees heard from the manufacturer that specific BMI ranges are likely to be included in the marketing authorisation, however these BMI cut off values are

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			unknown at present. Consultees agreed that it was not necessary to include specific BMI ranges in the scope if they are likely to be specified in the licence. The manufacturer stated that the issue of women of child-bearing potential had been resolved with the regulatory authority and that appropriate recommendations would be covered in the licence for this sub-group and this contraindication is unlikely to be included in the marketing authorisation.
	NHS Warwickshire	The population appears to be defined adequately. Both BMI and waist circumference are recommended objective measures for defining obesity, and are associated with clinical and pathological changes. BMI values of 30 kg/m^2 or above, or above 27 kg/m^2 with comorbid condition could be used. It might be that for people of South Asia origin a lower BMI cut-off may be required.	Comment noted. Consultees at the scoping workshop felt that it was not necessary to specify BMI ranges in the scope to differentiate between obese and overweight populations, as they are likely to be specified in the licence. The Committee will consider different BMI ranges for people from certain ethnic backgrounds in line with current NICE guidance documents (TA203 and CG87) for type 2 diabetes (which have included lower BMI

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			ranges for people from certain ethnic backgrounds, including people of South Asian family origin). The background section of the scope has been amended to include further information on BMI ranges for patients from certain family origins, in line with recommendations in TA203 and CG 87. The 'other considerations' section of the scope has also been updated to state 'the need for different BMI ranges for people from certain ethnic backgrounds will be considered'.
	VIVUS BV	The current appraisal objective is based on the proposed indication as submitted with the initial application, and may change based on the CHMP final opinion. Otherwise appropriate.	Comment noted. Recommendations will only be made in line with the final marketing authorisation.
Comparators	Arena Pharmaceuticals	The comparators appear appropriate. None should be described as best alternative care. In the event that the sponsor seeks approval for phentermine with topiramate in a restricted patient population, it will be important to assure that the comparators are evaluated in the proposed patient population. This may require subgroup analyses of the existing data for the proposed comparators.	Comment noted. No change to the scope required.
	NHS Warwickshire	The comparators are appropriate. However, given that lorcaserin is also subject to NICE appraisal, it might be more appropriate to appraise both through a Multiple Technology Appraisal process.	Comment noted. At the scoping workshop, the manufacturer of lorcaserin confirmed that the regulatory timelines for lorcaserin have

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			been delayed and therefore it will not form part of routine clinical practice in the NHS at the time an appraisal of phentermine with topiramate begins. Consequently, lorcaserin has been removed as a potential comparator from the scope.
	VIVUS BV	Orlistat is the only currently available licensed treatment in the UK. Lorcaserin is an investigational product – but we agree that these are the most appropriate comparators for pharmacotherapy. Perhaps it would also be worth considering assessment relative to the whole spectrum of behaviour modification, pharmacotherapies and bariatric surgery as this might provide some further useful contextual insights.	Comment noted. At the scoping workshop, the manufacturer of lorcaserin confirmed that the regulatory timelines for lorcaserin have been delayed and therefore it will not form part of routine clinical practice in the NHS at the time an appraisal of phentermine with topiramate begins. Consequently, lorcaserin has been removed as a potential comparator from the scope. Consultees agreed that behaviour modification alone was not an appropriate comparator for this appraisal as phentermine with topiramate was likely to be given after or in conjunction with behaviour modification, rather than replace it. Consultees also agreed that

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			invasive surgical procedures were not likely to be replaced by phentermine with topiramate, and therefore, were not relevant comparators. Consultees at the scoping workshop agreed that orlistat (both low and high dose preparations) was the most appropriate comparator for an appraisal of phentermine. The scope has been amended accordingly.
Outcomes	Arena Pharmaceuticals	Yes. It may also be appropriate to consider measures of glycemic control among patients with type 2 diabetes (glycosylated haemoglobin; fasting glucose). Other surrogate markers of cardiovascular risk may be appropriate (e.g., hsCRP). It may be appropriate to evaluate the impact of the agent on concurrent use of medications for hypertension, dyslipidemia, and/or diabetes. In the absence of cardiovascular outcomes data, the use of risk calculators that incorporate multiple of the "surrogate" markers to predict the net effect of the drug may be informative (e.g., Framingham or similar calculators).	Comment noted. Consultees at the scoping workshop agreed to include 'changes in concomitant medication' as an outcome measure and 'HbA1c' as a surrogate marker. The scope has been updated accordingly.
	NHS Warwickshire	The outcomes are appropriate. We assume that the main outcome measures are weight loss and maintenance of weight loss.	Comment noted. Consultees agreed that weight loss was a key outcome for an appraisal of phentermine with topiramate.
	VIVUS BV	To outcome measures we would propose adding "changes in concomitant	Comment noted. Consultees

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		medication use for the treatment of weight-related comorbidities (e.g. use of antihypertensive or antidiabetic medications)". For surrogate markers, we would propose addition of glycemic endpoints (glucose, HbA1c, fasting insulin), and for other endpoints would consider markers of liver function.	at the scoping workshop agreed to include 'changes in concomitant medication' as an outcome measure and 'HbA1c' as a surrogate marker. The scope has been updated accordingly.
Economic analysis	NHS Warwickshire	No comment.	Comment noted. No changes to the scope required.
	VIVUS BV	No specific comments.	Comment noted. No changes to the scope required.
Equality and Diversity	Arena Pharmaceuticals	None	Comment noted. No changes to the scope required.
	NHS Warwickshire	No equality issues identified.	Comment noted. No changes to the scope required.
	VIVUS BV	No specific comments. Has not been studied for use in children or adolescents (paediatric waiver in place). Not for use in pregnancy.	Comment noted. Consultees discussed whether women of childbearing potential are likely to be contraindicated to phentermine with topiramate. The manufacturer stated that the issue of women of child-bearing potential had been resolved with the regulatory authority and that appropriate recommendations would be covered in the licence for this sub-group and this contraindication is unlikely to be included in the marketing authorisation.
Innovation	Arena	Intentional weight loss of 5-10% is associated with medical benefits that	Comment noted. The

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	Pharmaceuticals	include decreased risk of type 2 diabetes, decreased blood pressure, improved lipid profile, reduced pain from osteoarthritis, and improved quality of life.[1] This could represent a step-change in the management of overweight and obese patients. [1]Executive summary of the clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults. *Arch Intern Med* 1998 September 28;158(17):1855-67.	manufacturer is encouraged to describe the innovative nature of phentermine with topiramate in their evidence submission. The Committee will consider this information during the course of the appraisal. No change to the scope required.
	VIVUS BV	We do expect that Qsiva will be viewed as a "step-change" or major innovation. Its demonstrated ability to produce 10% weight loss means that it fills a significant gap in available treatment options. Its use also generates a wide range of improvements across all clinical and quality of life endpoints and potentially minimises the burden of other comorbid conditions associated with excess weight and the medication use associated with treating these conditions. There is no currently available formally approved medicinal therapy option that can achieve a 10% weight loss. Most pharmacotherapies produce at most a ~5% weight loss, whilst bariatric surgical procedures can lead to 15% or greater weight loss. There is, however, a treatment gap for therapeutic options able to produce weight loss in the 5-15% range, which can potentially be addressed by Qsiva. This could provide an additional tool to address a significant public health concern, could then address an unmet need for treatment in the 5-15% weight loss range, and potentially decrease the need for surgery in some patients for whom 5% weight loss would not be considered sufficient to mitigate obesity-related health risks. Quality of life data (both weight-related and broadly health-related) were collected throughout the clinical program, and showed positive benefits on weight-related and physical functioning domains. Factoring in decreases in concomitant medication use/burden could also be helpful to allow examination of the entire benefit picture. These data have been collected in completed studies for use of antihypertensive medications, lipid-lowering medications, and anti-diabetic medications. Prevention of the progression	Comment noted. The manufacturer is encouraged to describe the innovative nature of phentermine with topiramate in their evidence submission. The Committee will consider this information during the course of the appraisal. No change to the scope required.

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		to diabetes is clinically important data which was collected and analyzed over the one- and two-year trial program. This is one of the key reasons for treating obesity, and should be an important component of the analysis.	
Other considerations	Arena Pharmaceuticals	Experience (i.e. safety/efficacy) of the drug and its individual components in other jurisdictions.	Comment noted. The Committee will consider the safety and clinical efficacy of phentermine with topiramate during the course of the appraisal. No change to the scope required.
Questions for consultation	Arena Pharmaceuticals	BMI should be used to specify the obese and overweight populations for consideration in this proposal (see "Population", above). Phentermine with topiramate should be used as recommended in NICE clinical guideline 43, with a possible restriction to a population that does not include women of child-bearing potential (topiramate is teratogenic). Further, use in patients at high risk of cardiovascular events may require restriction since phentermine can raise blood pressure. Given these potential safety-related use restrictions, it may be appropriate to restrict use of phentermine with topiramate to obese and overweight patients who have failed to achieve adequate weight reduction (e.g., at least 5%) with orlistat or lorcaserin (pending NICE appraisal), and to adjust the appraisal accordingly. The technology may be more clinically or cost effective in morbidly obese patients. As stated above, a population that excludes women of childbearing potential should be examined. Clinical trial data from pivotal trials of up to 108 weeks duration have been generated, and should be used for the appraisal. This technology should be appraised through the STA process.	Comment noted. The Committee will consider the safety and clinical efficacy of phentermine with topiramate during the course of the appraisal. No change to the scope required. Consultees discussed whether women of childbearing potential are likely to be contraindicated to phentermine with topiramate. The manufacturer stated that the issue of women of child-bearing potential had been resolved with the regulatory authority and that appropriate recommendations would be covered in the licence for this sub-group and this contraindication is unlikely to be included in the marketing

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			authorisation.
	VIVUS BV	BMI ≥ 27 kg/m2 with one or more obesity-related comorbidity(ies), or ≥ 30 kg/m2. Would expect Qsiva to be a first line pharmacotherapy, to be used in conjunction with lifestyle/behavioural intervention and a weight-reducing diet. The selected comparators are reasonable – orlistat as the available pharmacotherapy, and the investigational therapy lorcaserin with the closest near-term potential marketing authorisation. In our view, there are no other oral pharmacotherapies likely to become available within the next couple years. Qsiva was studied in a broad range of clinical patients, with comparable benefits seen across all populations. The largest studies were in patients with comorbidities, who saw significant benefits not only in weight loss but in endpoints for the weight-related comorbidities and medication use. From an efficacy and cost effectiveness perspective, this group might demonstrate the greatest benefit. However, all groups derived benefit and could be considered. We believe that Qsiva should be evaluated through a Single Technology Assessment, [redacted] (confidential information removed). Inclusion with lorcaserin as a multiple technology assessment, with that application being 12-18 months behind Qsiva, could potentially delay the availability of the assessment information significantly.	Comments noted. At the scoping workshop, the manufacturer of lorcaserin confirmed that the regulatory timelines for lorcaserin have been delayed and therefore it will not form part of routine clinical practice in the NHS at the time an appraisal of phentermine with topiramate begins. Consequently, lorcaserin has been removed as a potential comparator from the scope, and an MTA of phentermine with topiramate and lorcaserin is no longer possible as it would cause a significant delay in guidance being issued on the use of phentermine with topiramate.

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

Healthcare Improvement Scotland
Cochrane Peripheral Vascular Diseases Group

NATIONAL INSTITUTE FOR HEALTH CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Phentermine with topiramate for the treatment of obesity and overweight

Response to consultee and commentator comments on the provisional matrix of consultees and commentators (pre-referral)

Version of matrix of consultees and commentators reviewed: Provisional matrix of consultees and commentators sent for consultation					
Summary of comments, action taken, and justification of action:					
	Proposal:	Proposal made by:		Action taken: Removed/Added/Not included/Noted	Justification:
1.	Remove Overweight and Obesity Organisation from patient/carer group consultees	NICE Secretariat		Removed	The organisation has disbanded.
2.	Remove National Public Health Service for Wales from general commentators	NICE Secretariat		Removed	Organisational name change to Public Health Wales NHS Trust who are already listed on the matrix as general commentator.

3.	Add Royal College of Pathologists to professional group consultees	NICE Secretariat		Added	Royal College of Pathologists meets the inclusion criteria and has a close interest in this appraisal topic therefore this organisation has been added to the matrix as a professional group consultee.
4.	Add Allied Health Professionals Federation as a general commentator	NICE Secretariat		Added	Allied Health Professionals Federation meets the inclusion criteria and has a close interest in this appraisal topic therefore this organisation has been added to the matrix as a general commentator.
5.	Remove Diabetes Foundation from relevant research group commentators	NICE Secretariat		Removed	This organisation have merged with Diabetes UK who are already listed on the matrix as a patient/carer group consultee.
6.	Remove Arena Pharmaceuticals from comparator manufacturer commentators	NICE Secretariat		Removed	This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria.

7.	Add GlaxoSmithKline to comparator manufacturer commentators	NICE Secretariat		Added	GlaxoSmithKline has been identified as a comparator manufacturer for the appraisal topic and has been included in the matrix as a comparator manufacturer commentator.
8.	Add Teva UK to comparator manufacturer commentators	NICE Secretariat		Added	Teva UK has been identified as a comparator manufacturer for the appraisal topic and has been included in the matrix as a comparator manufacturer commentator.
9.	Remove NHS Clinical Obesity Group from general commentators	NICE Secretariat		Removed	The organisation has disbanded.