National Institute for Health and Clinical Excellence

Single Technology Appraisal (STA)

Lorcaserin hydrochloride for the treatment of obesity and overweight

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

Comment 1: the draft scope

Section	Consultees	Comments	Action
Background information	Royal College of Physicians	The information is currently reasonable, but really only focuses on metabolic / cardiovascular complications of obesity. Other complications that are equally important include arthritis, joint pain, breathlessness, sleep apnoea, mood disorders including anxiety and depression and increased risk of a wide range of cancers.	Comment noted. The background and outcomes sections are intended to provide a brief outline of the principle outcomes which measure health benefits and adverse effects that are important to patients and/or their carers. Depending on the evidence available other conditions (e.g. depressive and psychological disorders) may be captured under health related quality of life.
	Arena	No comments; information is accurate and complete.	Comment noted.

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	Pharmaceuticals		No action required.
	GlaxoSmithKline Consumer Healthcare	Since the remit is also addressing cost effectiveness of locaserin hydrochloride, we would recommend including a contextual statement to describe the disease impact of obesity in the United Kingdom.	Comment noted. The background section is intended as a brief outline of the disease area. The remit of NICE applies to England and Wales.
	National Obesity Forum	BMI is increasingly thought to be inappropriate in the clinical setting, and waist circumference is increasingly being used. It allows a better assessment of individual risk, and is more appropriate in S Asians. HSE 2010 showed 26% obesity. Should read 'i.e. bariatric surgery' rather than 'such as'	Comment noted. Waist circumference is included as an outcome in the scope. The scope has been amended to reflect the comment about bariatric surgery.
The technology/ intervention	Royal College of Physicians	Yes, reasonable although very brief. It would be helpful to piont out that 5HT2c receptors are found elsewhere in CNS and outside CNS. The evidence that hypothalamus is involved in 'macronutrient selection' in humans is non-existent and pretty weak even in rodents - it is perhaps best if this phrase omitted.	Comment noted. The technology section of the scope is intended as a brief description of the technology, and has been amended to reflect this comment.
	Arena	The technology could be somewhat more accurately described. In particular, the current description of the three lorcaserin Phase III clinical trials appears to indicate	Comment noted. The technology

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	Pharmaceuticals	that a different patient population was the focus of each of these trials. That is not the case. Two of these trials--BLOOM and BLOSSOM--enrolled adult patients without diabetes who were either obese (BMI 30 - 45 kg/m2), or who were overweight (BMI 27 - 29.9 kg/m2) and had one or more weight-related conditions--specifically, hypertension, dyslipidaemia, cardiovascular disease, impaired fasting glucose, or sleep apnoea. The third trial--BLOOM-DM--enrolled patients if they were either overweight or obese and had type 2 diabetes that was being managed with oral hypoglycaemic agents.	section of the scope is intended to include a brief description of the trials, and has been amended to provide greater clarity.
	GlaxoSmithKline Consumer Healthcare	It states that lorcaserin should be used in combination with behavior modification. It should also state that it should be used as an adjunct to a reduced calorie diet and increased exercise.	Comment noted. The technology section of the scope is intended as a brief description of the technology, and behaviour modification encompasses a reduced calorie diet and increased exercise. No change to the scope required.
Population	Royal College of Physicians	The population described covers those likely to have been included in the relevant trials but without full details of what patient subgroups (e.g. ethnicity, co-morbid conditions) and numbers in these subgroups were included in the trials it is difficult to know whether there will be sufficient information available to draw firm conclusions about risk / benefit in these subgroups.	Comment noted. Subgroups based on diabetes, glucose are included in the scope. The 'Other considerations ' section of the scope has been amended to reflect

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			the need for the appropriate adjustment of BMI for older people and for people of certain ethnic groups. The Committee will consider the evidence available during the appraisal process.
	Arena Pharmaceuticals	The population is defined appropriately. Within the population that was the focus of BLOOM and BLOSSOM, we believe an additional subgroup of interest (as suggested by NICE below, in "Other Considerations") is patients with impaired fasting glucose, as they are at high risk of progression to type 2 diabetes. Patients with diabetes are another subgroup of specific interest (and were the exclusive focus of one of the lorcaserin Phase III clinical trials [BLOOM-DM]).	Comment noted. During the scoping workshop, consultees agreed that people with type 2 diabetes and people with impaired glucose tolerance were important subgroups. They are part of the scope as subgroups for consideration.
	GlaxoSmithKline Consumer Healthcare	All three studies were conducted in patients with a BMI 27 and above. The revised EMA guidelines (2008) state that patients with >BMI 25 with one co-morbidity shold be considered for such studies. Only one randomized placebo-controlled trial has been conducted in patients with a BMI 25 to BMI 27.9. This 4 month study demonstrated significantly greater weight loss with the active drug as compared to placebo (Anderson et al 2006). There are no 6 or 12 month clinical trials that have examined	Comment noted. The appraisal will be conducted within the marketing authorisation of the

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		efficacy and safety in this lower BMI population. Since none of the lorcaserin trials included patients with a BMI below 27, consider a subset analysis in the overweight population (BMI 27-30). From these data, it may be possible to estimate predicted weight loss at the lower range of overweight.	product.
	National Obesity Forum	Needs S. Asian parameters specified	Comment noted. The 'Other considerations' section of the scope has been amended to reflect the need for the appropriate adjustment of BMI for older people and for people of certain ethnic groups.
Comparators	Royal College of Physicians	Yes, orlistat is a reasonable comparator. It seems unlikely that phentermine /topiramate will be licensed in Europe at the time of appraisal judging from recent information.	Comment noted. Phentermine with topiramate has received a negative CHMP opinion, and there is no evidence that it is used in established clinical practice outside its proposed licensed indication. It has been removed from the scope as a comparator.
	Arena	ORLISTAT (high-dose and low-dose): While orlistat is available in both high-dose (120	Comment noted.

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	Pharmaceuticals	mg) and low-dose (60 mg) formulations, the latter is sold exclusively as an over-the-counter product. To the best of our knowledge, low-dose orlistat is not typically used in clinical practice in England or Wales. We therefore do not believe that lorcaserin should be compared with low-dose orlistat. We agree, however, that high-dose orlistat is an appropriate comparator. QSIVA (phentermine/topiramate): On 18 October 2012, the Committee for Medicinal Products for Human Use (CHMP) adopted a negative opinion, recommending refusal of the marketing authorisation for the medicinal product, Qsiva, a fixed-dose combination of phentermine and topiramate, for the treatment of obesity. The CHMP had concerns about long-term effects of phentermine on the heart and blood vessels, and long-term psychiatric and cognitive effects of topiramate. Topiramate is also known to be potentially harmful to the fetus if taken by pregnant women. Because the CHMP recommended that Qsiva not be granted marketing authorisation, and because it is unlikely to be a marketed product at the time lorcaserin receives marketing approval, we do not believe that it is an appropriate comparator for an evaluation of lorcaserin.	Orlistat will be examined within its licensed indication. It is used in both high and low dose formulations in the UK.No action required. Phentermine with topiramate has received a negative CHMP opinion, and there is no evidence that it is used in established clinical practice. It has been removed from the scope as a comparator.
	GlaxoSmithKline Consumer Healthcare	A third weight loss candidate medicine, rejected by the US Food and Drug Administration in 2011, is a centrally-acting, fixed dose, prolonged release combination of naltrexone and bupropion. Four, 1-year studies have been conducted including one study in patients with Type 2 diabetes. The designs of the trials are similar to those of lorcaserin and may be another comparator. to consider.	Comment noted. It is not established in current clinical practice, and is therefore not considered a comparator for this appraisal.
	National Obesity Forum	Low dose orlistat (60mg) is not NHS prescribable.	Comment noted. Orlistat will be examined within its licensed indication. It is used in both

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			high and low dose formulations in established clinical practice in the UK, and has therefore been included in the scope. No action required.

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Outcomes	Royal College of Physicians	Most information will be derived from looking at weight loss, and markers of diabetes control /CV risk (BP /lipids). Changes in insulin resistance are of academic interest, but clinical relevance uncertain. QoL measures important and may help capture important information not specifically sought in trials. It would be useful to know about effects on joint pain / sleep apnoea but doubtful that this information exists.	Comment noted. The outcomes section of the scope is intended to provide a brief outline of the principle outcomes which measure health benefits and adverse effects that are important to patients and/or their carers. A number of outcomes and surrogate endpoints were agreed at the scoping workshop and are included in the scope. Depending on the evidence available, other conditions (e.g. joint pain and sleep apnoea) may be captured under health related quality of life.
	Arena Pharmaceuticals	Yes--we believe that these outcomes generally are relevant measures to consider in an evaluation of lorcaserin or any other treatment for overweight and obesity. We do not believe, however, that a count of the number of	Comment noted. The outcomes section of the scope is intended to provide a brief

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		conditions would have much substantive meaning. Each should be considered in its own right in terms of its impact on morbidity, mortality, and QALYs.	outline of the principle outcomes which measure health benefits and adverse effects that are important to patients and/or their carers. A number of outcomes and surrogate endpoints were agreed at the scoping workshop and are included in the scope.
	GlaxoSmithKline Consumer Healthcare	Consideration should be given to changes in different fat deposits e g., visceral adipose tissue. as compared to total fat mass. Change in concomitant medication may be included as an outcome since this can be an indirect marker assess cost effectiveness	Comment noted. The outcomes section of the scope is intended to provide a brief outline of the principle outcomes which measure health benefits and adverse effects that are important to patients and/or their carers. A number of outcomes and surrogate endpoints were agreed at the scoping workshop and are included in the scope. Change in concomitant medication has been added as an outcome to the scope.
	National Obesity Forum	weight loss, waist circumference (not hip), and % losing 5% and 10% of body weight. CV outcomes and mortality unrealistic, and insulin resistance probably superfluous.	Comment noted. The outcomes section of the scope is intended to provide a brief outline of the principle outcomes which measure health benefits and adverse effects that are important to

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			patients and/or their carers. A number of outcomes and surrogate endpoints were agreed at the scoping workshop and are included in the scope to capture the long term outcomes. Weight loss percentages are covered under the current outcome of weight loss, and will be considered according to the evidence. Hip circumference has been removed as an outcome from the scope.
Economic analysis	Royal College of Physicians	Obesity is a chronic condition, and long-term management (including with drugs) is often needed. Time horizon should reflect this and model for long term (5 years or more) treatment, and/or for intermittent treatment - ie restart in those in whom significant weight gain occurs after stopping therapy - this may better reflect real world use of such drugs rather than unrealistic 'single course' of therapy (where weight regain is very likely) or continuous therapy for many years which may not be acceptable to patients.	Comment noted. The NICE guide to the methods of technology appraisal states that it is essential to consider the clinical and cost effectiveness over an appropriate time horizon (section 5.1.3). No change to the scope required.
	Arena Pharmaceuticals	We are in agreement with the guidance stipulated for reference cases in general, and that it applies to lorcaserin.	Comment noted. No action required.
Equality	Royal College of Physicians	If there is sufficient information on benefits in different patient groups (e.g. by ethnicity) that would be useful, but doubtful this information is available.	Comment noted. The ‘Other considerations‘ section of the scope has been amended to reflect the need for the appropriate adjustment of BMI for older people and for people of certain ethnic groups.

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	Arena Pharmaceuticals	Not applicable.	Comment noted. No action required.
Other considerations	Royal College of Physicians	It would be interesting and relevant to look at efficacy in those with more severe obesity (BMI > 35 or 40) separately, as this group are often in greater need of treatment. Analysis of those with multiple co-morbidity / high symptom burden in terms of improvements in both efficacy, effects on metabolic and QoL outcomes would be useful.	Comment noted. The appraisal will be conducted in line with the remit from the Department of Health and within the final marketing authorisation.
	Arena Pharmaceuticals	We agree that persons with type 2 diabetes and those with impaired fasting glucose are relevant subgroups. The lorcaserin economic model will, among other things, consider the value of therapy in these two specific subgroups.	Comment noted. No action required.
	GlaxoSmithKline Consumer Healthcare	If examining impaired glucose tolerance, consideration should be given to the number of patients who shifted from a classification of impaired glucose tolerance at baseline to normal at one year, i.e., shift analysis. Since patients with metabolic syndrome are costly to a health care system, consider examining these individuals as a subgoup.	Comment noted. The Committee will consider the evidence made available.
	National Obesity Forum	should read 'ethnic'	Comment noted. The scope has been amended accordingly.
Questions for consultation	Royal College of Physicians	The drug is innovative but from trial information available in the public domain is unlikely to offer a step change in obesity management (efficacy appears similar to orlistat). However, it may be useful for some patients as different mechanism of action offers potential treatment for some who cannot take orlistat.	Comment noted. The manufacturer may describe the innovative nature of lorcaserin in their evidence submission. The Committee will consider this information during the course of the appraisal. No change to the scope required.
	Arena	(1) We consider lorcaserin to be innovative in its potential to improve the	Comment noted. The

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	Pharmaceuticals	management of overweight and obesity. Lorcaserin is a first-in-class weight loss drug that we expect will be approved for long-term use. Currently, the only marketed prescription product for the treatment of overweight and obesity is orlistat. While orlistat is effective, it is notorious for its most frequently reported side effect--oily, loose stools. We believe that the gastrointestinal side effects of orlistat have constituted a significant impediment to its widespread use for the management of overweight and obesity. (Orlistat also interferes with the absorption of fat-soluble vitamins and other fat-soluble nutrients [e.g, patients taking warfarin, which binds to vitamin K, must be carefully monitored]). A 2011 Israeli study by Hemo et al. of more than 7000 patients taking sibutramine (no longer on the market) or orlistat reported a two-fold greater risk of discontinuation among the latter group; fewer than 10% of all patients initiating treatment with orlistat were on therapy at the end of one year, and fewer than 2% were on therapy at the end of two years. Lorcaserin has much better tolerability than orlistat, and in clinical trials of at least one year in duration, 8.6% of patients treated with lorcaserin prematurely discontinued treatment due to adverse events, compared with 6.7% of those receiving placebo. (2) While we believe that the above-described differences in tolerability between lorcaserin and orlistat are clinically important, incorporation of such considerations into the calculation of QALYs is challenging due to data limitations. Of particular note, many of the orlistat clinical trials used a run-in period to select patients who were expected to be more compliant with therapy; none of the lorcaserin trials used a run-in. Rates of discontinuation from orlistat and lorcaserin clinical trials therefore cannot be compared directly. We will attempt to capture differences in tolerability between lorcaserin and orlistat in our QALY calculations, but we think this exercise will be largely speculative in the absence of truly comparative data. (3) Until lorcaserin is on the market and used in clinical practice, it will be difficult to determine how compliance and persistency would differ between patients treated with orlistat versus lorcaserin. We believe, however, that lorcaserin's substantially better tolerability profile (v.s. orlistat) will have a substantial impact in clinical practice on the treatment of overweight and obesity.	manufacturer may describe the innovative nature of lorcaserin 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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	National Obesity Forum	Phentermine and diethylpropion are routinely used in clinical practice, but mainly only in the private sector. However, because of the Qsymia trials, it is potentially time for a reappraisal of phentermine, as there is now more patient exposure data to allow an adequate safety and tolerability review. Change in concomitant medication shouldn't be included, because it is impossible to say whether a drug was correctly or inappropriately withdrawn in patients who still have residual high risk. S. Asians are the most important specific group. Any weight related co-morbidity should be included, although the 'obesity paradox' suggests that certain groups such as post MI should not be considered for weight reduction. This is innovative and will make a step-change, by potentially doubling the number of agents clinicians have for helping manage obesity and its co-morbidities.	Comment noted. Comparators will only be included in the scope if they are used routinely in the NHS. According to the British National Formulary, Phentermine and diethylpropion are not recommended for the treatment of obesity. No action required. 'Change in concomitant medication' has been added as an outcome to the scope. The 'Other considerations ' section of the scope has been amended to reflect the need for the appropriate adjustment of BMI for older people and for people of certain ethnic groups. The manufacturer may describe the innovative nature of lorcaserin in their evidence submission. The Committee will consider this information during the course of the appraisal.
Any additional comments	Royal College of Physicians	No other comments	Comment noted. No action required.

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

Roche Products Limited
The Royal College of Nursing
Department of Health

NATIONAL INSTITUTE FOR HEALTH CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Lorcaserin hydrochloride for the treatment of obesity and overweight

Response to consultee and commentator comments on the matrix of consultees and commentators

Version of matrix of consultees and commentators reviewed: 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.	Removal of Vivus as a comparator manufacturer	NICE secretariat		Removed	This organisation is not considered a comparator manufacturer for this appraisal. Vivus has been removed from the matrix as a comparator manufacturer commentator.
2.	Removal of Cardiovascular Diseases Specialist Library as a research group	NICE secretariat		Removed	This organisation is no longer in operation.