.**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

SINGLE TECHNOLOGY APPRAISAL

APPEAL HEARING

Advice on naltrexone-bupropion for managing overweight and obesity [ID757]

Decision of the panel

Introduction

1. An appeal panel was convened on 27 October 2017 to consider an appeal against NICE's final appraisal determination, to the NHS, on naltrexone-bupropion for managing overweight and obesity [ID757].

2. The appeal panel consisted of:

• Professor Alan Silman	Chair
• Professor Sheena Asthana	Non-Executive Director
• Dr Kevin O'Shaughnessy	Health Service Representative
• Patrick Hopkinson	Industry Representative
• John Morris	Lay Representative

3. None of the members of the appeal panel had any competing interest to declare.

4. The panel considered appeals submitted by Orexigen Therapeutics Ireland Limited.

5. Orexigen Therapeutics Ireland Limited was represented by:

• Grant Castle	Partner Covington & Burling LLP
• Dr Amy Halseth	Vice President, Clinical Development and Medical Affairs. Orexigen
• Mark Nuijten	Ars Accesus Medica

6. In addition the following individuals involved in the appraisal were present and available to answer questions from the appeal panel:

• Professor Iain Squire	Appraisal Committee Vice Chair –Technology Appraisal Committee (TAC) A (chair for this appraisal)
• Dr Jane Adam	Appraisal Committee Chair – TAC A
• Janet Robertson	Associate Director
• Hamish Lunagaria	Technical Analyst
• Sabine Grimm	Evidence Review Group (ERG) representative, Kleijnen Systematic Reviews

7. The appeal panel's legal adviser - Stephen Hocking, DAC Beachcroft LLP - was also present.

8. Under NICE's appeal procedures members of the public are admitted to appeal hearings and several members of the public were present at this appeal.

9. There are two grounds under which an appeal can be lodged:

   Ground One: In making the assessment that preceded the recommendation, NICE has:
   a) Failed to act fairly
   b) Exceeded its powers.

   Ground Two: The recommendation is unreasonable in the light of the evidence submitted to NICE.

10. The Vice Chair of NICE (Dr Rosie Benneyworth) in preliminary correspondence had confirmed that Orexigen had potentially valid grounds of appeal as follows:

    - Ground 1a – NICE has failed to act fairly

    - Ground 2 – the recommendation is unreasonable in the light of the evidence submitted to NICE

11. The appraisal that is the subject of the current appeal provided advice to the NHS on naltrexone-bupropion for managing overweight and obesity [ID757].

12. Before the appeal panel inquired into the detailed complaints the following made a preliminary statement: Mr Grant Castle on behalf of the Orexigen and Professor Iain Squire on behalf of the appraisal committee (AC).

Appeal by Orexigen

Ground 1a - In making the assessment that preceded the recommendation, NICE has failed to act fairly

1a.1 - NICE presented an ICER for the first time only in the FAD, which means that the company has not had the opportunity to comment meaningfully on the Institute's view of the cost-effectiveness of Mysimba. This is inconsistent with NICE's procedures and unfairly prejudiced Orexigen.

13. Mr Grant Castle stated that the most appropriate approach to calculating the ICER was discussed at length with the ERG and Orexigen at the first AC meeting, and that the ERG had had a number of concerns over the modelling provided by the company and the uncertainties it raised. However, the Company felt these warranted further exploration in the open discussions that would be possible if a second appraisal consultation document (ACD) had been issued. They thought they addressed the ERG concerns in the revised modelling presented after the first AC meeting and ACD. From the appellant's perspective, the ACD was about the committee's concerns about the modelling. It did not serve to inform the appellant about what a likely ICER might be.

14. He referred to a document produced for the appeal hearing that showed how the company perceived differences in the thought processes present in the ACD and the subsequent FAD. This emphasised what he believed were fundamental revisions that meant that further consultation by way of a second ACD was needed. The lack of the second ACD denied the company the opportunity to discuss how Mysimba's use might be revised, for example, by restricting its use or with new stopping rules. By not being able to comment further (through a second ACD), NICE was being procedurally unfair and was not acting in a transparent way. This was particularly important where the final ICER was close to the threshold for automatic approval. The appellant wished to say that the true ICER was lower than that adopted by the committee with the result that some of the committee's concerns about uncertainty would no longer be relevant.

15. Professor Squire for NICE, commented on the processes between the ACD and FAD. He stated that the committee were convinced of the clinical efficacy of Mysimba based on the trials presented. The trials were, however, of short duration, but emphasised they were not of "too" short a duration. Their shortness meant that the committee were not convinced of the longer-term efficacy of Mysimba to reduce weight beyond 56 weeks. They thought that long-term (continuous or intermittent dosing) would be required but they had no idea what proportion of the treated population this would represent and the demographics of this population would be important in determining this.

16. He emphasised that the first base-case and model submitted by the company to the ERG did not allow a meaningful ICER to be generated for the committee. By recoding the software, the company did provide a tool (running on VBA) that was usable by the ERG for modelling after the ACD was published. The committee understood the recoded model to be essentially the original model, with some but not all requested changes made. For example, in the revised base-case the company had still failed to implement reversion to base line BMI after stopping the drug, preferring instead the less conservative approach of age-adjusted BMI. It was possible to generate an ICER (against standard management alone) with the model close or even below the £20K threshold, but it was extremely sensitive to inputs into the model. He emphasised the AC's concern that the modelling was too uncertain for cost-effectiveness decision making.

17. The AC had also heard from general practitioners that if Mysimba was made available it would be used without the availability of tier-3 services (weight management services including adjunct drug treatment) and Mysimba's proven efficacy in the CPOR trials rested on it being used in conjunction with these services. Hence, there was a concern that demand was likely to be very high and in an environment where it's efficacy was uncertain.

18. He further emphasised that the AC was following NICE's own guidance (section 6.3.3) in ensuring that the evidence available was robust and being cautious in its interpretation when faced with the huge uncertainty around the ICER.

19. Finally, he commented on the document provided by Grant Castle about the difference between the ACD and the FAD. Professor Squire noted that the AC

could only consider the cost-effectiveness of Mysimba after Orexigen provided a tool to generate a valid ICER following the ACD's publication. He was, therefore, not surprised that the ACD and FAD appeared to offer different perspectives.

20. Professor Squire was asked if it were likely that new evidence would emerge to inform the decision process. He replied that uncertainties in the modelling was based largely on the clinical trials and thus he thought that new data was unlikely to remove those uncertainties. The modelling was very sensitive to even small changes in the QALYs and the QALYs themselves were qualitatively very small (amounting to tens of days).

21. The NICE team were asked if there was any precedent for an ICER being introduced for the first time in an FAD. Janet Robertson for the NICE team said she would be surprised if this had not happened before, but could not give an example where an ICER had previously appeared for the first time in the FAD.

22. The appeal panel chair asked that given ICERs can go up and down had the committee fully considered all possible scenarios? The NICE team said it had and added that they felt the second AC meeting had been a very open forum to discuss the company's ICER results in a very frank way. This was especially true of the weight trajectory after stopping Mysimba. What was focused on in this meeting were the uncertainties that the modelling had provided.

23. The appellants felt that having generated an ICER of close to the £20K threshold using conservative modelling, (which they thought had been acknowledged), it would be relatively easy to come in under this figure with further data (that they had) and refinements to the modelling if they had been given a further chance to do so. They had not actually done further modelling to prove this.

24. The appellant was asked what this new data was and they stated it was data from open label trials looking at cardiovascular impact showing that weight reduction was maintained beyond the 56 weeks of the COR trials.

25. The appellant was asked whether the NICE team had considered this data. Professor Squire for the NICE team said that all the evidence presented to them was considered. The issue of the weight trajectory after stopping Mysimba still lacked any evidence. He emphasised again that the COR trials were not too short, but of short duration. Hence, they were not helpful in deciding on long-term efficacy for a cost-effectiveness evaluation.

26. The appeal panel chair asked for clarification on a point from the NICE team. Namely, given an ICER close to the £20K threshold, how would the AC factor in the large uncertainty in the modelling?

27. Professor Squire replied that they followed the guidance provided by 6.3.3 of the NICE methods guide when faced with uncertainty in an ICER i.e. when faced with uncertainty in an ICER they would be more cautious in their assessment. The company could have reduced some of the uncertainty by including co-morbidities in their modelling but had not done so.

28. Mark Nuijten for the appellant thought that the uncertainties raised would not greatly affect the ICER. However, they would need to perform sensitivity analysis to confirm this and this had not been done.

29. The appeal panel chair asked the NICE team just how much further modelling is reasonable. Dr Jane Adam for NICE said there were, of course, timing constraints but NICE had been very constructive in their feedback after the first AC meeting. However, it was Orexigen who had come back with a figure of around £23K for the ICER (with standard management as comparator).

30. Grant Castle for the appellant summarised the exchange that had occurred to this point. NICE had accepted there were significant changes between the ACD and FAD. He questioned whether the AC meeting was an appropriate venue for frank and open debate. Furthermore, it was not open to all the public in the way that a second consultation would have been. He pointed out that as a public body any decision made by NICE that impacted a company must be reached in an open and transparent way. NICE should listen to both the company but also to the wider stakeholders to serve the public interest.

31. The company was asked why they had not replied to the £23K ICER presented at the second AC meeting. Mark Nuijten replied that they had not done so as they had fully expected that a second ACD would be forthcoming, and this would give them the opportunity to submit formally a follow up report and revised modelling.

32. The chair asked if Orexigen had been surprised by the appearance of the FAD and Mark Nuijten said they had been.

33. Janet Robertson for NICE said this appraisal had followed the usual course and timetable laid out by NICE. She also said that the NICE process did not necessarily involve indefinite numbers of iterations. However, there is a provision for a company to slow the appraisal timeline, for example, if the company have new trial data that might be imminently available. There was no request from Orexigen for such a slowing of the appraisal process.

34. The appeal panel concluded as follows: –

35. This is not a case of a defective first consultation exercise. It was not suggested (and if it was suggested the appeal panel would not have agreed) that the consultation on the ACD was itself flawed. The committee had provided as much insight into its thinking as it was able under the circumstances, and consultees had been enabled to make an intelligent response. That consultation, so far as it went, was correctly carried out.

36. Instead the question in the appeal panel's opinion was whether fairness generally or NICE's methods guide specifically required a second round of consultation. The appeal panel noted that both the requirements of fairness and NICE's methods guide treat a requirement for a second consultation as very much the exception to the rule. Indeed, it has been said that a "fundamental" difference between what has been consulted on and what is subsequently proposed is

needed before reconsultation is obligatory. In this exceptional or unusual case a requirement to reconsult can arise.

37. The appeal panel also reminded itself that if an essential element that should have been consulted on was omitted from a first consultation, then the obligation to reconsult will arise even if the proposal has not changed fundamentally.

38. The appeal panel accepted that it is very unusual for an ICER to appear for the first time in the FAD. However, this was not a situation of the committee's making. Orexigen were aware that an ICER was being considered by the AC (and an ICER had been provided by Orexigen) and because they had provided the economic model they would have had a sense (albeit imperfect) of where possible ICERs might be. The appeal panel were not persuaded that an intelligent response on cost efficacy was impossible.

39. This was not a case where a preferred ICER was withheld from the appellant. Nor was it a case where an essential element that had to be consulted on had been withheld. There is no absolute requirement in NICE's methods guidance for ICERs to appear in an ACD prior to appearing in an FAD, (although if a sufficiently robust ICER can be generated at the ACD stage it should be included). Additionally, although it is generally understood that an ICER is a key element in the cost-effectiveness evaluation, the ICER is an output rather than an input. An ICER cannot be argued for in isolation. Instead, changes in inputs (or modelling) that will affect the ICER can be advanced. The appellant was well able to comment on all of the inputs that might drive an ICER. If it was the case that they could not perform sensitivity analyses to understand which of those inputs were the most important, the fault lay with them as the creators of the first iteration of the model.

40. The panel then asked whether what was proposed had changed so significantly that fairness demanded a second consultation. It concluded that this was not the case. Although the ACD and the FAD differ significantly, the panel agreed that this was inevitable. At the ACD stage the committee could do no more than express its reservations about the modelling (which it had done in some detail); only at the FAD stage was it able to quantify those concerns for the first time. The substance of what was being discussed in the FAD had not changed significantly, and barring points of detail neither had the committee's reservations.

41. The appeal panel therefore dismissed the appeal on this point.

Ground 2 – the recommendation is unreasonable in the light of the evidence submitted to NICE

2.1 The Appraisal Committee's conclusion that the relevant clinical trials are too short to eliminate uncertainty is unreasonable.

42. Grant Castle opened for the appellant Orexigen saying that NICE had not accepted the views of the CHMP (and FDA) on what the CHMP considered the requisite trial duration (of 12 months) to be adequate for the review process. The COR trials had actually run for 56 weeks. The courts in the Servier court ruling

had said that if NICE in its appraisal process deviates from CHMP it must justify its position, and it had failed to do so.

43. Professor Squire replied for NICE saying that that they were not contradicting the CHMP. The requirements of the AC were distinct from the CHMP. The data from the COR trials was not "too short" but it was of insufficient duration to inform the cost-effectiveness decision to recommend (or not) Mysimba.

44. Sabine Grimm for NICE confirmed that longer-term data was available (up to 104 weeks for weight loss) and was used in the review process.

45. Professor Squire emphasised that clinical efficacy was not being questioned. The issue was the considerable uncertainty around cost-effectiveness and the short-term nature of the COR trials did not remove that uncertainty.

46. The appeal panel chair asked if the maintained weight reduction after stopping was modelled. Professor Squire said that it is up to the company to provide the modelling and scenarios. The key debate was what would happen to the BMI after stopping Mysimba and it was the trajectory of weight gain after stopping Mysimba that lacked any certainty. The conservative assumption it went back to baseline was the committee's preferred one, but Orexigen had chosen to model a return to age-related BMI instead. Sabine Grimm confirmed that weight loss maintained on lifestyle and exercise alone (standard management) was incorporated into the current ICER estimates.

47. The appeal panel chair also asked if the committee had considered recommending for research only in its FAD. Professor Squire confirmed they had.

48. The appeal panel concluded as follows: –

49. On the issue of trial duration, the appeal panel agreed that when the FAD (3.7) states that they (the COR trials) were of short duration the AC were using this in the sense of the trials were too short to inform robustly an analysis of the long-term cost-effectiveness of Mysimba. Trial duration as defined by CHMP (or the FDA) was for a distinctly different process: to inform the balance of efficacy and safety of a product for a marketing authorisation. In the Servier case, the court thought that a post-hoc subgroup analysis of a clinical trial accepted as scientifically valid by the CHMP had been rejected as scientifically invalid by NICE. Here both the CHMP and NICE accepted that the trial produced valid data, but the uses made of the data differed between the two bodies. One found it adequate for their task and the other did not. This does not require explanation, as the different roles of these bodies are well understood. Hence, the appeal panel did not think the AC were acting unreasonably or contracting the CHMP and its requisite trial duration (of 12 months) for their review process.

50. The appeal panel therefore dismissed the appeal on this point.

2.4 It is unreasonable to prejudice the company on the basis of budget impact where the potential budget impact is a result of a failure of CCGs to implement

a treatment pathway for obese patients consistent with NICE clinical guidelines.

51. Grant Castle opened for the appellant, commenting on the concern they thought the AC had shown over budget impact. He emphasised that tier-3 services (weight management services including adjunct drug treatment) were under threat with >80% having been lost nationally. This meant that the committee's view that Mysimba would represent a large budgetary impact was unreasonable as it would be prescribed in the small and contracting remainder of tier-3 services.

52. Professor Squire for NICE said that the AC member (who could not be present today but emailed the AC to confirm this point) confirmed that he was certain Mysimba would be used by GPs outside of tier-3 services and expected as a result a very significant take up by GPs. Hence, there was the potential for considerable budgetary pressure.

53. Dr Jane Adam for NICE pointed out that Orexigen's original submission referred to an eligible patient population in England of 4 million patients although further enquiry by the panel established that in fact the company had assumed a treated population of approximately 20,000.

54. Dr Amy Halseth for Orexigen said that the US experience was that only a small core of specialist GPs prescribed the majority of Mysimba. She agreed it should be used only as an adjunct to manage cravings. In the US, perhaps only 2% of eligible patients actually receive Mysimba.

55. The chair of the appeal panel asked whether the resources to deliver tier-3 should be taken into account. He also asked specifically and hypothetically whether the AC would have been concerned by huge budgetary costs (if there would have been any) had they been convinced of the cost-effectiveness of Mysimba.

56. Professor Squire for NICE replied emphatically that they would not have had regard to budget. It was primarily the considerable uncertainties in the cost-effectiveness that drove their decision in the FAD. If they had felt there was a robust and acceptable ICER they would have recommended use without regard to budget impact.

57. NICE were asked if there were any offsets to the tier-3 costs. Professor Squire said that tier-3 costs were not assessed as they were outside the scope of the TA. NICE also cannot mandate the CCGs to provide them. Mysimba was only proven to work (based on the COR trials) when these services were available. Their lack meant that large numbers of patients could be prescribed the drug without this key service being in place.

58. The appeal panel concluded as follows: –

59. The appeal panel thought that the AC were convinced of the efficacy of Mysimba in reducing body weight. What they were not convinced of was its cost-

effectiveness and this directly related to the issues with the ICER and modelling provided by Orexigen. It was clear that budgetary pressures had not swayed their decision, if they had been persuaded of the cost-effectiveness of Mysimba they would have recommended it regardless of budget impact. They also faced an issue that tier-3 services were no longer widely available and likely to contract further. Without this framework, Mysimba may well be prescribed in an environment where its efficacy was compromised (all the trials had been carried out using Mysimba as adjunct to tier-3-like services) adding to the uncertainty about cost-effectiveness. NICE cannot mandate the provision of these services, but the contribution their absence makes to uncertainty is a relevant concern for the committee. Since the AC repeatedly emphasised their uncertainty about the cost-effectiveness case for Mysimba, the appeal panel felt that the AC had not acted unreasonably in their FAD judgement as regards budget impact.

60. The appeal panel therefore dismissed the appeal on this point.

Conclusion and effect of the appeal panel's decision

61. The appeal panel dismissed the appeal against this appraisal on all grounds.

62. There is no possibility of further appeal against this decision of the appeal panel. However, this decision and NICE's decision to issue the final guidance may be challenged by applying to the High Court for permission to apply for a judicial review. Any such application must be made within three months of NICE publishing the final guidance.