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Dr Rosie Benneyworth

Vice Chair

National Institute for Health and Care Excellence

By Email: 4 September, 2017

Dear Dr Benneyworth

Re: Appeal against Final Appraisal Determination for naltrexone-bupropion for managing overweight and obesity

Thank you for your letter dated 21 August 2017, providing your initial view on the above appeal points. We are also grateful for you confirming the date for responding as being 5 September 2017.

Response

We are pleased that points 1.(a).1 (Ground 1(a)) and 2.4 (Ground 2) are valid. Specifically on point 1.(a).1 (Ground 1(a)) and the reference to NICE's procedures, you note that we will need to persuade the Panel that the decision not to issue a second ACD was unfair. In that connection, and as you will see below, a number of the points raised as standalone appeal grounds also are highly relevant when discussing the failure to consult adequately on the ICER and the need to issue a second ACD. Your initial scrutiny letter suggests in several places that we should raise certain points under this valid ground and we intend to do so. However, we have also indicated below a few other areas that, in our view, would also fall as discussion points under this ground and are relevant in persuading the Panel of the prejudice caused to the company by not issuing a second ACD (e.g., budget impact, clinical trial duration, stopping rules and so forth).

Our detailed comments on the remaining (non-accepted) points are as follows:

Ground 1(a)

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1.(a).2 - NICE's failure to give Orexigen an opportunity to consult on any proposed ICER, or to provide any justification, means that process has also lacked transparency.

We do not agree with the rationale which you say makes this point fails as a standalone valid appeal point. You do, however, suggest that this point and the arguments associated with it can be made under 1.(a).1. We therefore reserve our position that the process lacked transparency and was unfair but, in the spirit of cooperation, agree to proceed on this suggested basis and raise these issues under 1.(a).1.

1.(a).3 - NICE's assumption that treatment with Mysimba must inevitably involve long-term and recurrent treatment is counter to the product's approved summary of product characteristics (SmPC), which is inconsistent with NICE's procedures and unfairly prejudices the company.

We note that you do not consider this to be a valid appeal point and that long-term or recurrent treatment could be within the scope of the SmPC. We think that some of the subtleties of this point may have been missed from the initial scrutiny, including the Committee's assessment based on inevitability of long-term or recurrent treatment and the failure to consider stopping rules. However, we are mindful of the need to narrow the issues as far as possible and avoid protracted correspondence. We therefore reserve the right to raise the failure to consider stopping rules and related aspects, which could have been addressed as part of a proper consultation that could also have impacted the ICER, under point 1(a)1 and we shall make the point under that ground.

1.(a).4 - The Appraisal Committee has allowed the NHS's failure to offer tier 3 services in accordance with NICE clinical guidelines to influence its approach to this HTA, which is procedurally unfair and prejudices the company.

Your view is that this point is similar to Ground 2.4 and, hence, in order to narrow the issues we shall make the point under accepted Ground 2.4.

Ground 1(b)

- NICE has exceeded its powers by making a determination based wholly or mainly on budget impact.

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The budget impact aspect is clearly also related to consultation on the ICER and hence we intend to raise this point as something that deserved consultation around the ICER under Ground 1(a) (point 1(a)1).

Ground 2

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

The initial scrutiny letter does not address adequately our specific point that that the finding in the FAD that the trials were of "short duration" is unreasonable given that they (the trials) were one year plus. Also that the Committee has failed to explain why it reaches this view and why it diverges from the CHMP's opinion. We ask that this is considered a valid appeal point and in the alternative that we may bring this point up as part of our discussions on Ground 1(a) (point 1.(a).1) in particular in discussions over ICER consultation.

2.2 - NICE's assumption that treatment with Mysimba must inevitably involve long-term and recurrent treatment is inconsistent with the product's approved summary of product characteristics (SmPC), and is therefore is unreasonable in light of the evidence before it.

For the reasons set out at our response to 1.(a).3 above, we intend to discuss this point at the appeal as part of the ICER discussion under point 1(a)1.

2.3 - The Committee's over-cautious assessment of uncertainty was unreasonable in light of the evidence before it.

We kindly ask that you reconsider the validity of this point. In particular for the following reasons:

- We consider that the model was the most conservative possible. The company was guided to this highly conservative position by the Committee. No provision has been made for the fact

that any changes are likely only to result in an ICER reduction and, in this specific case, the model is very sensitive to even small changes in quality of life such that a significant reduction in ICER is likely in such cases. To take only this high-water mark, which was reached only on the Committee's guidance, is over-cautious, unreasonable in light of the evidence and failed to take account of the impact on quality of life.

- An appropriate reaction to any perceived uncertainty would have been a range of ICERs. We consider that this range would include a number of ICERs that fell under the £20,000 threshold and that would have taken account of the sensitivity relating to quality of life markers, with the £23,750 representing the uppermost. In this way, any uncertainty is limited (to a particular range) and capped at £23,750. The failure to provide a range and to take an over-cautious assessment of risk is unreasonable.

- This (range) approach would have provided a good degree of certainty, which is one of the factors for consideration by the Appraisal Committee mentioned at 6.3.3 of the Guidance.

- Whilst it is correct that the Committee, in its FAD, noted that Mysimba "could be considered innovative" for reasons expressed elsewhere in this response and our appeal letter, it is not clear whether and to what extent this innovative aspect was taken into account. It appears weighted against uncertainty which, as explained above, could be limited and capped.

- Therefore, as set out in our appeal letter, Mysimba meets at least four out of the five factors in the Guidance at 6.3.3. We reiterate our position that the Committee has failed to exercise its discretion in light of these factors and this was unreasonable.

2.5 - Given that the evidence before the Appraisal Committee is that the level of care offered at tier 3 is patchy and diminishing, it is unreasonable for the Committee to conclude that the introduction of Mysimba into tier 3 would have a large impact on NHS budgets.

As per the points above, the budget impact issue is something that we would expect further consultation around the ICER and which should have resulted in a second ACD. We intend to make this a discussion point under our valid Ground 1(a) (point 1(a)1). We are also aware that it is not the role of Appraisal Committees to make judgements on matters relating to budget impact in any case, so this issue should not have arisen.

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We welcome any further comments you have in respect of the above response. In the meantime, thank you for confirming that the appeal is to be heard at a public meeting of the Institute's Appeals Panel (Spring Gardens, London), on 27 October 2017. We will confirm by separate correspondence the names of the people who will be representing Orexigen at this hearing.

Yours sincerely

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Orexigen Therapeutics Ireland LLC