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OREXIGEN®

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

Orexigen Therapeutics Ireland, Ltd. (together with its affiliates, "Orexigen", the "company") wishes to appeal the Final Appraisal Determination ("FAD") for naltrexone-bupropion ("Mysimba") in managing overweight and obesity on the following grounds:

- Ground 1.(a) - NICE has failed to act fairly;
- Ground 1.(b) - NICE has exceeded its powers; and
- Ground 2 - the recommendation is unreasonable in light of the evidence submitted to NICE.

It is possible to raise some of the concerns below under either of these grounds (1(a)/(b); or 2). Where the Institute has acted both in a procedurally unfair manner and an unreasonable manner, we raise them under both of these grounds.

Executive Summary

In summary, Orexigen challenges the refusal to recommend Mysimba for the following reasons:

Ground 1(a)

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.
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.
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.
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.

Ground 1(b)

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

Ground 2

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

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

The company provides the detail in the main body of this letter below. Before doing so, the company wishes to provide some relevant background and context.

The Management of Obesity in England and Wales

It is clear from the documents submitted and generated during this appraisal, including the ACD and FAD, that the level of care that the NHS offers to overweight and obese patients in England and Wales falls below the standard that NICE envisages in Clinical Guideline 189 (Obesity: identification, assessment and management). In particular, a large number of CCGs are not commissioning tier 3 services, where drug therapy supplements existing interventions, such as life-style management. Where CCGs have offered tier 3 services in the past, some are in the process of decommissioning them. The Committee heard testimony from CCGs and clinical experts, who explained that there is "patchy" - or "post-code" - availability of tier 3 services. It also heard evidence about the significant issues with the only available drug treatment (INN orlistat). These issues include the fact that orlistat is pharmacologically unacceptable, lacks efficacy and is not tolerated due to its unpleasant gastrointestinal side-effects. Since the NHS is currently expected to reimburse what is in effect a product that offers poor value for money, this has led to poor compliance with the NICE guidelines. NICE, its clinical expert advisers and patient organizations, have all made clear that this has resulted in an unmet clinical need.

Given these circumstances, the introduction of any new clinically-effective well-tolerated medicinal product for the management of obesity - must inevitably lead to CCGs having to allocate new funds to offer care in accordance with Clinical Guideline 189. This obviously has the potential to impact NHS budgets which, the record shows, is clearly a major concern for the Appraisal Committee.

The company considers that concerns about potential budget impact has driven the Appraisal Committee's approach to this HTA, including the restrictive assumptions it has applied and the limited extent to which it is willing to exercise any discretion, e.g. to reward innovation or accept even limited uncertainty, even though the ICER is close to the £20,000 threshold. The simple point is that if CCGs were already commissioning tier 3 care to reflect the clinical guidelines, budget impact would be limited. The company should not be penalized for a non-functioning treatment pathway.

The Committee will be acutely aware that such failures to commission and/or moves towards decommissioning leads in turn to inequalities in both type and quality of care (so-called "postcode prescribing") which the Institute was designed to eliminate. The company would expect that the Institute would seek to address such differential and reportedly poor standards of care by ensuring that there are appropriate alternatives to meet a recognized patient need, rather than using that need as a basis for a restrictive approach to the assessment.

Grounds of Appeal

Ground 1.(a) - NICE has failed to act fairly

Ground 1.(a).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.

The key determinant of whether the Institute will recommend a product as a cost-effective use of NHS resources is the product's ICER relative to the £20,000 threshold. It is therefore fundamental to any meaningful consultation process that stakeholders should understand the Appraisal Committee's view of the possible ICERs and the effect that changes in inputs and assumptions have on those values.

At the pre-ACD stage, discussions between the Institute and Orexigen were centered almost entirely around perceived defects in Orexigen's model. The ACD did not therefore contain any ICER values. For example, one of the ERG's key concerns was that the company's model operated using DICE, which resulted in slow run-times and meant that it was overly time-consuming for the ERG to run sensitivity analyses. Orexigen re-programmed the model using Visual Basic to address this and also addressed (some at its own volition) other issues, so that both the ERG and Appraisal Committee subsequently deemed the model to be an acceptable basis for decision-making.

It nevertheless remained clear that changes to the model, including inputs, population, comparator, treatment pathway and associated assumptions, could influence the ICER significantly. Indeed, slides presented at the second Appraisal Committee meeting suggested a range of ICERs between £6,507 and £207,274. The company therefore had a legitimate expectation that the Appraisal Committee would engage in a meaningful consultation (for example a further meeting, or second ACD - see below) on any proposed ICER, or ranges of ICERs, before issuing a FAD.

Clearly, going from an ACD that contained no ICERs and focused on concerns with the company's model, to a FAD based on a model that all agreed was an acceptable basis for decision-making, represented a substantial development. At a minimum, therefore, the Committee should have issued a second ACD (in accordance with 3.7.31 the Guide to the Process for Technology Appraisal). That ACD could have explained the Committee's views on the company's ICERs, including subgroup analyses, and then explained the ERG's and Appraisal Committee's preferred approach, including the results of any sensitivity analyses. It also could have helped to clarify any unresolved issues including uncertainties, which were raised during the second meeting. Instead, it proceeded without consultation to a FAD.

The Committee's failure to give the company any visibility as to the ICERs that it was using as the basis of its decision-making in an ACD has denied the company the opportunity to engage in any meaningful way. Given that decisions are usually driven by the ICER, the company has had no opportunity to comment or present evidence which may have influenced the Committee's recommendation. This was procedurally unfair and prejudiced the company's position.

Ground 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.

Not only did the Institute fail to consult on any proposed ICER, but the FAD does not contain justification for the ICER that the Appraisal Committee ultimately selected. This means that the assessment process lacks transparency.

Section 3.20 of the FAD contains only a single ICER for naltrexone–bupropion with standard management compared with standard management alone, *i.e.* "£23,750 per QALY gained." The FAD contains no explanation of the basis for this figure. Given that the ICER is very close to the threshold at which reimbursement is usually recommended by an Appraisal Committee, it would be particularly important for the company to understand the basis for this figure.

NICE's Guide to the methods of technology appraisal provides that the "credibility" of the Institute's guidance is "*dependent on the transparency of the Appraisal Committee's decision-making process*" and it is "*crucial that [its] decisions are explained clearly*" (para 6.1.9). The guide also states (at para 6.1.10) that the "*need for clarity in explaining how the Appraisal Committee has come to its conclusions*" is a governing principle. Without an understanding of the basis for the ICER figure, and the reasons for the Appraisal Committee's reliance on it, the appraisal process for Mysimba lacks transparency and clarity, and the credibility of the Appraisal Committee's guidance is undermined.

Ground 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.

The assumption of long-term and recurrent treatment is inappropriate given Mysimba's approved SmPC. NICE is obliged to appraise products consistent with a product's marketing authorization. The Mysimba SmPC presumes that patients would receive an initial 16 weeks treatment, after which treatment must stop for patients who have not achieved at least a 5% reduction in weight. The SmPC also makes no provision for recurrent treatment of patients who fail to respond or cease therapy for any other purpose. Rather, it presumes that therapy will continue only for patients who continue to respond. NICE should have reflected this in its assessment, and its failure to do so was procedurally unfair.

It would have been more consistent with Mysimba's marketing authorization and NICE's procedures to include appropriate safeguards or limitations in any recommendation, such as stopping rules after 16 weeks or precluding recurrent use.[1]

[1] It is noted that comments on the ACD from an NHS professional received via the NICE website also suggested stopping rules.

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.

Testimony to NICE highlighted that there was a "clear" and "significant" unmet need for a product like Mysimba, which means that it will potentially impact a large number of patients. For example, the Registrar for the Royal College of Physicians stated: *"There is **significant** unmet need...a **strong patient voice** that is asking for this"* because *"[orlistat] is not tolerated by **a very high proportion** of patients."* An NHS professional with relevant expertise in diabetes and obesity also described the lack of therapeutic options in obesity in the UK as *"**startling**"* demonstrating a *"**significant** unmet need."* This professional also described the use of orlistat as *"**incredibly limited** by GPs or specialists and is poorly tolerated"* and implored the Committee to recommend Mysimba to impact upon the *"**obesity epidemic.**"* A representative on behalf of the Royal College of Pathologists also stated "*There is a **clear clinical need** for novel pharmacological approaches to treatment of overweight and obesity*" and stressed the need for novel treatments (such as Mysimba) "*to be available within a **cohesive** four tier pathway.*"[2]

Having received these comments (on the ACD), the Committee in its FAD made numerous references to, and justified its recommendation on, the basis of "high" unmet need/patient numbers (see FAD para. 1.2 (end), paras. 3.1, 3.2, 3.3 and 3.17). Its reasons for refusing to recommend Mysimba included the "potentially large patient population" and "large impact on NHS resources" (para. 1.2 (end), paras. 3.3, 3.14, 3.17 and 3.20).

The Committee accepted that Mysimba is efficacious, potentially innovative and that there is an unmet clinical need for novel pharmacological approaches to treatment. The latter is due largely to the poor clinical take-up and undesirable side-effects of the only existing overweight/obesity drug treatment (orlistat) recommended as pharmaceutical treatment option at tier 3 of the treatment pathway for obesity in NICE clinical guideline 189.[3] The Committee heard from a clinical expert that CCGs and other bodies have been decommissioning "already patchy" tier 3 services.

The result of this non-compliance with NICE's guidelines is that any positive recommendation for Mysimba would inevitably have a significant impact on NHS budgets. The Appraisal Committee has used this potential budget impact as the basis for its considerations at paras. 3.16 and 3.17 of the FAD, in which it advocated a cautious approach and an unwillingness to accept even limited uncertainties or the exercise of any discretion. This is despite the cost-effectiveness of Mysimba being close to the £20,000 ICER threshold.

In essence, this means that companies launching products that fit within an NHS treatment pathway that is malfunctioning would be disadvantaged relative to a product introduced into a treatment pathway that

[2] These comments also reflect the pre-ACD testimony from clinical and patient experts, which highlighted failings in NHS treatment of obesity, for example noting "geographical variation", a need to provide "more comprehensive services", and a "real gap"/no "middle ground" in NHS obesity service.

[3] Namely tier 3 of the guideline on obesity: identification, assessment and management.

is functioning. In the latter case, the budget impact would necessarily be less because commissioners have already allocated budget to treat patients in that pathway.

It is procedurally unfair to allow the failure of CCGs to deliver care in accordance with NICE guidelines to prejudice the company.

It is worth noting in this respect that section 6.2.14 of Methods Guide states that "[i]*n general*" the Committee "*may*" require more robust evidence on cost-/effectiveness, but it is not mandatory. Similarly, the Methods Guide indicates that, as the potential budget impact increases, the Committee will want to be "*increasingly certain*" of cost-effectiveness. However, it does not *require certainty*. At para. 3.17 of the FAD the Committee is express that it "*needed to be certain*" of value to the NHS, which is inconsistent with its procedures. Given the cause of the budget impact is inappropriate "postcode prescribing" and NICE's remit to eliminate such inequalities of care, NICE should clearly have accepted less than total certainty. In any event, we are concerned that the Institute has based its decision primarily due to budget impact and we take this point up briefly below as a separate ground of appeal.

Moreover, neither the ACD nor the FAD provides any explanation for the Appraisal Committee's conclusion that the introduction of Mysimba will have a large budget impact. The process therefore lacks transparency. Indeed, there are arguments that the patchy provision of services at tier 3 means that the product cannot have a large impact on NHS budgets (see Ground 2(5) below).

Ground 1(b) -NICE has exceeded its powers by making a determination based wholly or mainly on budget impact.

For the reasons stated above in Ground 1(a), we consider (subject to greater transparency and reasoning being forthcoming) that the Appraisal Committee based its decision largely on budget impact considerations. As indicated above, whilst we accept that concerns over budget impact may require greater certainty, the Methods Guide states that the potential budget impact "*cannot determine*" the Appraisal Committee's decision. To do so would, in our view, mean that NICE has gone beyond the scope of its powers by applying an affordability test when its functions under section 233 of the Health and Social Care Act 2012 require NICE to conduct a cost-effectiveness assessment having regard to the "broad balance between the benefits and costs." Whilst it has always been clear that this has been the position of NICE historically, we are mindful of the fact that the ability for NICE to make budget impact determinations is currently subject to judicial review per *R (otao Association of the British Pharmaceutical Industry) v National Institute for Health and Care Excellence* (CO/2936/2017), lodged 21 June 2017, and we reserve the right to supplement or amend this ground pending further developments in that case and also on understanding in more detail the reasoning for the decision. This could be achieved through a second ACD, for example.

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

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

Guidance from the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) makes clear that pivotal clinical trials for obesity drugs should be one year in duration:

> *"Weight loss has often been observed to plateau after 5 to 6 months of continuous treatment with currently or previously available pharmacological treatments. However, at least 12 month duration of the majority of the confirmatory trials is recommended to fully document the effect on weight development and obesity related comorbidities."*[4]

The U.S. Food & Drug Administration (FDA) imposes similar standards. The majority of the clinical trials underpinning the efficacy of Mysimba are 56 weeks in duration and therefore exceed these standards.[5] Moreover, the length of trials for Mysimba also exceed or at least equaled the duration of those which NICE deemed acceptable for orlistat.

It is therefore unreasonable to expect that a manufacturer developing an obesity drugs to conduct longer studies, since this would effectively mean that no new obesity drug is ever likely to meet NICE's standard for evidence.

While the company accepts that NICE is not bound to accept the CHMP's position, the Court in *R (Servier) v National Institute for Health and Clinical Excellence* provided that the Institute must give valid reasons for deviating from the position of bodies such as the CHMP. In effect, the Appraisal Committee should have explained why the CHMP was wrong to conclude that "*at least 12 month duration of the majority of the confirmatory trials* ...[can]... *fully document the effect on weight development and obesity related comorbidities*", which it has not done. The process therefore also lacks transparency which is not in accordance with NICE's procedures (see 6.1.9 and 6.1.10 of the Guide to the methods of technology appraisal).

Ground 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.

The assumption of long-term and recurrent treatment is inappropriate. NICE is obliged to appraise Mysimba consistent with its approved SmPC, which specifies 16 weeks treatment, then cessation of treatment for patients who have not achieved at least a 5% reduction in weight. The SmPC also makes no provision for recurrent use in patients who have ceased to use Mysimba, either because they have failed to respond to, or have not tolerated, the product. Its failure to do so was unreasonable.

A more reasonable approach - and one that is more consistent with the SmPC and the evidence before it[6] - would be to consider appropriate safeguards, such as stopping rules or a recommendation precluding recurrent use.

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[4] CHMP Guideline on clinical evaluation of medicinal products used in weight management, available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/07/WC500209942.pdf.

[5] It is noted that although not a core dataset, the NB-CVOT study was used for modelling purposes and this contained data up to 158 weeks.

[6] See for example the NHS professional's comments on the ACD received via the NICE website.

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

The company has submitted the results of four large phase III clinical trials, which the Committee accepts constitutes robust evidence of Mysimba's effectiveness.

The company approached the Institute with a model and assumptions that it considered to be conservative, which produced an ICER of around £14,000 per QALY gained. The company then proceeded to accept all of the ERG's and Committee's suggested modifications to render the model even more conservative. In doing so, the company considers that it has taken the most conservative and restrictive position possible to determine the ICER.

It seems highly likely that, in reality, many of the other co-morbidities that have not been modelled into the manufacturer's submission would apply in a real world setting. Any of these would generate additional QALYs and the likelihood is that the true ICER would be closer to or actually below £20,000.

Although a lack of transparency means the company is not entirely clear of the precise basis for the ICER cited in the FAD (£23,750 per QALY gained), it seems clear that this must represent the "high water mark" based on the Appraisal Committee's preferred base case and conservative modelling inputs and assumptions. Given how sensitive the model is to changes in QALYs, any less conservative assumptions, which would be likely to lead to QALY gains, could be expected to reduce the ICER considerably.

Given this, and that the high water mark exceeds the £20,000 ICER benchmark by only a small amount, the level of risk to budget associated with any uncertainty is in reality very modest and the Committee has been unjustifiably and unreasonably over-cautious in its assessment of budget risk to the NHS (see below).

The Committee acknowledges that Mysimba is potentially innovative. Innovation is one of the factors set out at section 6.3.3 of the Guide to the methods of technology appraisal, which the Committee is required to take into account when determining whether a product is an effective use of NHS resources. It is noteworthy that Mysimba also meets all of the other relevant factors, with the exception of end of life. Given the above, this is clearly a situation where the Committee should have exercised its discretion to reward the innovative nature of the technology and recognized the influence of other factors (in accordance with 6.3.3 and 6.3.4 of the Guide to the methods of technology appraisal). It did not do so and this was unreasonable.

Ground 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.

As discussed above, a large number of CCGs are not commissioning services at tier 3 in the NHS treatment pathway for obesity and some are in the process of decommissioning them. This is largely because CCGs consider that NICE-recommended orlistat does not meet clinical needs of patient reaching tier 3.

The introduction of any new medicinal product that addresses an unmet need caused by the failure to deliver an appropriate level of care, must inevitably mean that CCGs will be required to allocate new funds to ensure patients receive care to an appropriate standard.

This potential budget impact has clearly driven the manner in which the Appraisal Committee has approached this appraisal, and it is unreasonable to penalize the company because of the failure of CCGs to commission services in accordance with existing guidelines.

Ground 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 with the very low number of surgical interventions in tier 4, the Appraisal Committee heard extensive evidence that the NHS is not offering widespread care for obese patients in tier 3 and that the number of CCGs funding such care is diminishing. This means that the introduction of Mysimba into tier 3 could not have a large impact on NHS budgets. It is unreasonable for the Committee to assume that it would, particularly without providing any explanation for this (see Ground 1(a).4 above). It appears that the Committee may have based this assumption on a hypothetical scenario that does not reflect the current realities of treatment in the NHS, as reflected in the evidence, which is unreasonable.

Based on the above, the company requests that any appeal is heard at a public meeting of the Institute's Appeals Panel.

Yours sincerely,

Director
Orexigen Therapeutics Ireland, Ltd.