Dear Donna

Thank you for the opportunity to comment on the appraisal consultation document for the above single technology appraisal.

I have received comments from colleagues in the Department of Health as follows:

"Taking each question in turn posed in the consultation documentation:

1. It does appear the relevant research evidence available for the use of nalmafene has been taken in to account. It appears that more consideration may be needed on the evidence for the current delivery of the relevant 'treatment as usual' interventions in primary and secondary care services (see 5 below).

2 The summaries of clinical and cost-effectiveness appear to be reasonable interpretations of the evidence referred to but it would be helpful to clarify certain areas of ambiguity.

a) It appears the alcohol consumption entry criterion for the 3 main studies was, in those identified with at least mild dependence, a drinking level of 60g/day or more (7.5 units) for men and 50g/day or more (5 units) for women 'FOR AT LEAST 6 DAYS IN THE LAST 28 DAYS prior to enrolment' [paraphrased]. It would be helpful to be clear if the populations used for the studies (or those agreed "post hoc analysis") were, in fact, mainly regular daily or daily high risk drinkers, or otherwise some indication of what their average daily consumption was. It is not easy to make a judgement about applicability of the normal 'treatment' comparator provided (of brief interventions or extended brief interventions in primary care) without greater clarity about the actual consumption profiles of the populations in the studies. It is also not clear how those 'enrolment' alcohol consumption criteria of the ESENSE and SENSE studies, or perhaps more usefully the actual consumption levels reported in those studies, relate to the description in para 3.16 (and in Table 1) concerning the WHO definitions of 'high' and 'very high' drinking risk levels - that was used for modelling (possibly including costs). The Table 1 itself does not make clear whether that risk level definition applies to a subject if even only one day in 28 has a drinking level over 60g/day (or 40g/day), or whether this is the mean daily level across the 28 days, or whether it is something in-between (see below). If a substantial proportion of the ESENSE/SENSE study subjects did drink substantially less than a measure of 'regular' daily drinking above high-risk drinking levels, it would be useful to discuss whether this could substantially affect the estimated harms and hence anticipated benefits that is achieved by the clear additional reduced consumption achieved with nalmafene? Assuming this has already been considered in the modelling, or even if it is not actually relevant, it would be helpful to be quite explicit about this. It should be made clear whenever 'high risk' drinking levels or above is mentioned in different parts of the analysis that the definitions are the same or suitably close throughout. Certainly, a current reader of the consultation document could not be

confident that the risk definitions are equivalent in different parts of the narrative. As noted, even the table 1, WHO definition, does not make clear whether this refers to 'every day' drinking'. Whilst the 1st column includes the phrase 'applies to a single day', which makes this appear to refer to a single 'binge drink' level, the risk threshold levels (in g/day) appear to follow the literature drawn from mortality and morbidity risk curves which are normally used for regular drinkers. This needs clarifying for the reader. If the diagnosis of 'dependence' is the element in the studies (and in the recommendations of the Appraisal) that effectively squares this circle in capturing the in-need population that can benefit, which appears likely to be the case assuming the modelling is correct, this should probably be more explicit, and the threshold for diagnosis should be clearer. Otherwise, it appears there is a risk that nalmafene may become misunderstood to have been proven to be useful in virtually any high risk and binge drinkers including those drinking at relatively modest levels; and it may lead to misunderstanding of the WHO definitions without greater clarity.

b) Although there were 2 GPs on the Appraisal Committee, it also appears that there has been no input from primary care as consultees and commentators. Given the apparently central assumption about what constitutes current practice in the provision of psychosocial interventions for this target population in primary care, and this relies on a reasonably robust understanding of this question, it appears the lack of wider input to the group could be a serious gap that should be addressed before having confidence in the analysis and especially in deciding speed of implementation that is feasible. If what is provided or available in primary care is very substantially less than the BRENDA psychosocial intervention in the studies, or not provided at all, does this undermine confidence in the likely effectiveness of nalmafene, particularly as the comparator study participants will have also engaged in additional demands of a research study (and we note the references to very high drop-out rates anyway)? It may be worth being explicit whether the recommendation relies on the assumption about what primary care currently provides being correct, or whether the technology will be considered cost-effective even if many GP practices would de novo have to initiate availability of such an intervention for this population. As noted, if this is a relevant question, it may need consideration from a wider group of primary care experts that has not yet provided evidence to the expert group.

There are 2 elements to the key studies, to the Marketing Authorisation and to the NICE recommendations that would benefits from further clarity - how is it anticipated that primary care practitioners will identify the threshold point for dependence (as noted above). The data presented in this Appraisal consultation document of the studies does not provide any of the detail of the actual drinking profile of the subjects in the studies to assist practitioners in understanding the drinking profile of the actual population that would be likely to benefit from their intervention, which profile seems likely to have been substantially affected by the need for a diagnosis of dependence.

4 We do not have any additional suggestions to make concerning the lack of any specific considerations identified to ensure avoidance of unlawful discrimination.

5. Given the requirement for relevant health bodies normally to provide funding to ensure that the health technology is available within 3 months, we note that these recommendations may only be feasible if the infrastructure for the delivery of the relevant psychosocial interventions will be in place to meet this timescale.

It does appear to be crucial to engage with primary care bodies such as the RCGP and the BMA to establish the current situation of provision and responsibilities under the General Medical Services contract, in order to be able to make a judgement about whether reasonable implementation of the technology could take substantially longer than 3 months.

In order to meet the need identified by NICE to provide this treatment predominantly in primary care, a delay may be necessary to establish the relevant pathway(s) in/with primary care; and for any additional training or staff needed (if this is not currently in place).

It should also be noted that some primary care services currently consider all pharmacotherapy for management of dependence is a specialist treatment and may not consider this incorporated in their core GMS contract - and, if so, they may request secondary care services to prescribe on an ongoing basis (or at least to initiate prescribing and to provide on-going advice). Whilst this is not directly relevant to the clinical effectiveness of the technology, it may be important to commissioning, to organisation of care pathways, and to costs.

In addition, some 'secondary care' community specialist alcohol services are the ones currently commissioned to provide suitable psychosocial interventions for those with alcohol dependence who do not need pharmacologically assisted withdrawal - whether for controlled drinking or for abstinence. These psychosocial secondary care services may not currently have any in-house access to prescribing and so the commissioners would be likely to need time to establish new pathways with secondary addiction services or with primary care. Any shift in entry criteria, and hence demand, may not be easy for some secondary providers to address at short notice, especially if new commissioning arrangements are needed.

This TA could also have an impact on scale of referral to prescribing specialist addiction services that currently are not funded to meet the needs of this population by their commissioners. It may not be possible to alter such care pathways in the usual 3-month timescale for funding of a NICE TA, particularly as the impact of this change may go considerably wider than the estimated prescribing costs to structural changes in provision of psychosocial care (with new staffing and training needs).

Currently, there is no clinical need for primary care practitioners precisely to diagnose mild dependence thresholds. Depending on the potential importance of this

diagnostic threshold alongside assessing drinking levels for identifying the eligible population, some specific support may be needed for primary care practitioners concerning what tools to use for this purpose (CAGE, AUDIT score, other...)".

Many thanks and best wishes

[redacted]
Department of Health