NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Nalmefene for reducing alcohol consumption in people with alcohol dependence

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Consultee	Comment	Response
Lundbeck	Lundbeck Limited ("we") would like to thank the Appraisal Committee for the opportunity to comment on the Appraisal Consultation Document (ACD) for nalmefene. To the best of our knowledge, we believe that the Appraisal Committee has taken all relevant evidence into account. We confirm that the summaries of clinical and cost-effectiveness are reasonable interpretations of the evidence and believe that the provisional recommendations form a sound and suitable basis for guidance to the NHS.	
	Section 2.1 "…adult patients with alcohol dependence who have a high drinking risk level without physical withdrawal symptoms and who do not require immediate detoxification'." -	
	We would also propose that the equivalent units of alcohol are added for clarification: 7.5 units or more a day for a man and 5 units or more a day for a woman.	Comment noted. The FAD has been updated to reflect this comment. See FAD section 2.1
	"Nalmefene is administered orally as 18mg film-coated tablets. The maximum dose is 1 tablet per day". - Please amend this paragraph to read: "Nalmefene is administered orally as 18mg film-coated tablets **and taken each day that the patient is at risk of drinking alcohol.** The maximum dose is 1 tablet per day."	Comment noted. The FAD has been updated to reflect this comment. See FAD section 2.4
	Section 3.2 "Psychosocial intervention (in the form of BRENDA) was provided to all treatment groups in the 3 studies." –	Comment noted. The FAD has been updated to reflect this comment. See FAD section 3.2
	We think it would be helpful for commissioners and prescribers to clarify here that	

Consultee	Comment	Response
	BRENDA is a non-disease specific approach which focuses on enhancing motivation, behavioural change and adherence to treatment.	
	Section 3.3 "A heavy drinking day was defined as alcohol consumption of 60 g/day or more (equivalent to 7.5 units or more) for men and 40 g/day or more (equivalent to 5 units or more) for women." – We believe it is important to clarify that the heavy drinking day (HDD) thresholds used in the clinical trials are in accordance with the WHO classification of drinking risk levels.	Comment noted. The FAD has been updated to reflect this comment. See FAD section 3.3
	Section 3.4 "…Patients were then instructed to take 1 tablet (the maximum daily dose)…" – Please amend this sentence to read "…Patients were then instructed to take 1 tablet (the maximum daily dose) **on an as-needed basis**…	Comment noted. The FAD has been updated to reflect this comment. See FAD section 3.4
	Section 3.9 "The treatment difference in the changes from baseline to 6 months in the number of heavy drinking days was −3.7 days per month (95% confidence interval [CI] −5.9 to −1.5, p=001) in ESENSE1…" – There is a typographical error in the p-value; the correct value is p=0.001.	Comment noted. The FAD has been updated to reflect this comment. See FAD section 3.9
	Section 3.16 "The 1-year cycle aimed to take account of treatment efficacy and patient adherence…" – Please correct this sentence to read: "The 1-year **short-term model** aimed to take account of treatment efficacy and patient adherence…"	Comment noted. The FAD has been updated to reflect this comment. See FAD section 3.16
	Section 3.26 "The average cost of psychosocial intervention at £4145 was taken from NICE clinical guideline 115" – Please correct this sentence to read: "The average cost of **secondary care inpatient-assisted withdrawal** at £4145 was taken from NICE clinical guideline	Comment noted. The FAD has been updated to reflect this comment. See FAD section 3.26

Consultee	Comment	Response
	115” **Section 3.30** “In all 3 situations, nalmefene plus psychosocial intervention dominated psychosocial intervention alone” – “In **both** situations (**9A and 9B**), nalmefene plus psychosocial intervention dominated psychosocial intervention alone”	Comment noted. The FAD has been updated to reflect this comment. See FAD section 3.30
	Section 3.33 “The ERG stated that the evaluation carried out in the model does not meet that specified in the final scope and that it was difficult to know how the results would apply to people receiving different forms and frequencies of psychosocial intervention.” – In order to keep this section 3.33 consistent with the discussion at the Appraisal Committee (section 4.9), we suggest the following text could be added to avoid confusion: “The ERG stated that the evaluation carried out in the model does not **fully** meet that specified in the final scope and that it was difficult to know how the results would apply to people receiving different forms and frequencies of psychosocial intervention. **However, the ERG was also of the opinion that the scope cannot be fully evaluated.**	Comment noted. This update was not considered appropriate as the comment was not reflected in any of the ERG’s documentation.
	Section 3.34 “The ERG had concerns about the generalisability of the population in the 3 nalmefene studies to clinical practice in England. People with severe psychiatric comorbidities were excluded from all 3 nalmefene trials, and those with severe medical comorbidities were excluded from the ESENSE trials. The manufacturer commented in its submission that many people with alcohol dependence also have diagnosed medical conditions and/or psychiatric comorbidities. Patients were also excluded from the nalmefene trials if they were taking certain medication, such as drugs for angina, anticoagulants, anticonvulsants, insulin, sedatives and systemic steroids. The ERG stated that the safety and efficacy of nalmefene in people taking these drugs was therefore uncertain. Only a small number of trial patients were from the UK (SENSE trial only, 5 sites out of a total of 156) and the manufacturer did not provide any data on the variability of the outcomes for different European countries. The ERG stated that the generalisability of this data for England was unknown.” -	

Consultee	Comment	Response
	We would like to reiterate the following points: 1. In the SENSE clinical trial, including in the five UK trial sites, nalmefene was allowed in patients with stable psychiatric co-morbidity and/or who were taking co-medication. 2. The decision whether or not to treat with nalmefene has to be taken by the treating physician on an individual basis. 3. The nalmefene clinical trials were multi-national studies conducted in 19 countries. Nevertheless, the SENSE study included patients from the UK, and these trials are likely to be generalisable to the UK population given that they captured data on different drinking patterns and cultures across Europe. 4. A comparison of patient baseline characteristics in the nalmefene trials to the United Kingdom Alcohol Treatment Trial (UKATT) in which almost half of patients opted for alcohol reduction as their treatment approach, suggests that patients were reasonably comparable in terms of age, sex, ethnicity, level of alcohol consumption at study baseline, and level of unemployment (see Godfrey C. Cost effectiveness of treatment for alcohol problems: findings of the randomised UK alcohol treatment trial (UKATT). BMJ 2005;331(7516):544-48; Heather N, Adamson SJ, Raistrick D, Slegg GP. Initial preference for drinking goal in the treatment of alcohol problems: I. Baseline differences between abstinence and non-abstinence groups. Alcohol and alcoholism 2010;45(2):128-35).	Comments noted. The Committee concluded that the baseline characteristics of the populations in the 3 studies (ESENSE 1 and 2 and SENSE) were not wholly generalisable to clinical practice in England, but provided sufficient evidence to allow clinicians to determine the patient population for treatment with nalmefene and psychosocial support. See FAD section 4.4
	Table 2, Comparison 3 "The manufacturer did not comment on the likely cost effectiveness of delayed initiation of nalmefene for people whose alcohol dependence did not respond to psychosocial intervention as recommended in NICE clinical guideline 115, compared with immediate initiation of nalmefene for all patients." – We reiterate that we have no clinical data on the use of nalmefene in people whose alcohol dependence did not respond (first) to PI and thus did not feel able to comment on the cost-effectiveness or otherwise of a delayed initiation strategy.	Comment noted. No action required.
	Section 4.6 "The Committee agreed that the relative effectiveness of nalmefene plus psychosocial intervention and naltrexone plus psychosocial intervention was uncertain." – We propose amending this sentence to read: "The Committee agreed that the	Comment noted. The FAD has been updated to

Consultee	Comment	Response
	relative effectiveness of nalmefene plus psychosocial intervention and naltrexone plus psychosocial intervention was uncertain, **due mainly to limitations in the available evidence base for naltrexone in people with mild alcohol dependence."** **Section 5.1** "Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication. " – In response to the specific question posed by NICE in the covering letter to the ACD, we do not believe that any extension to the normal period of 3 months is necessary for the following reasons: **1. Nalmefene is already being prescribed in the UK**. • Nalmefene has been licensed for use in the NHS in the UK since May 2013. The Scottish Medicines Consortium and the All Wales Medicines Strategy Group accepted nalmefene for NHS use in accordance with its licensed indication in November 2013 and January 2014, respectively. • Nalmefene is therefore already being prescribed in clinical practice in England, Wales and Scotland (in both primary care and in specialist settings for suitable patients). **2. Nalmefene is suitable for primary care initiation and prescribing.** • Continuous psychosocial support can be delivered by any healthcare professional and would be comparable to delivering an intervention at the level of an extended brief intervention or 'motivational interviewing' during regular and ongoing patient assessment visits. • The ACD acknowledges that the usual psychosocial intervention provided in clinical practice for mild dependent patients was brief advice or extended brief advice (4.1, p25). The ACD also acknowledges (4.4, p 27) that the clinical specialists' view was that although BRENDA was not used in its entirety in clinical practice, most of its components are provided in the form of brief interventions or extended brief interventions. Finally the committee was satisfied that BRENDA closely represented current clinical practice in England (4.9, p31).	reflect this comment. See FAD section 4.7 Comments noted. NICE's Guidance Executive considered the specific circumstances for which it would be appropriate to extend the standard 3 month funding period for relevant health authorities to comply with the recommendations. The Guidance Executive decided that the circumstances were not sufficiently met, and therefore the 3-month funding period was appropriate. Comments noted. No action required.

Consultee	Comment	Response
	3. Practical implementation of this guidance should not be difficult if the NHS bodies and Local Authorities responsible adopt a pragmatic mindset. • Although the Appraisal Committee has heard from clinical experts that the recommendations for the provision of psychological support in CG115 are considered to be aspirational, and not reflective of actual clinical practice, the approval of nalmefene allows healthcare professionals to offer a higher level intensity option to treat alcohol dependence than is currently offered in a primary care setting. • The Committee accepted that although NICE clinical guideline 115 recommends a specific intensity, duration and frequency of psychosocial intervention, the usual psychosocial intervention provided in clinical practice was brief or extended brief interventions and that both the duration and frequency of these interventions were shorter than that recommended in NICE clinical guideline 115 (section 4.1). The Committee also noted that BRENDA, as described in the three nalmefene studies, most closely resembled current established practice rather than best practice (section 4.4). • Specialist care is not needed to deliver BRENDA-level interventions. GPs and nurses already offer brief advice to patients with alcohol-related problems; they are sufficiently trained, and have the skills base and competence to deliver BRENDA-level interventions (such as extended brief interventions or motivational interviewing) in primary care. This is also supported in NICE CG115 which states that extended brief interventions would be an appropriate level of psychological intervention for treating mild dependence in a generalist tier 2 setting (Raistrick 2006, P85 CG115 full). • The nalmefene Summary of Product Characteristics (SmPC) requirement for continuous psychosocial support should be considered part of a standard clinical interaction and not a significant change from what would be delivered in common practice. Continuous psychosocial support is a simple intervention and is very similar to what is commonly used in routine clinical practice for the management of other long-term or chronic conditions, such as diabetes, where the patient's involvement in decisions about his or her own management and care is important. The psychosocial support needed is similar in level of intensity and duration to a brief intervention or extended brief intervention, as NICE itself has acknowledged. • Finally, as noted above, nalmefene is already being prescribed in the NHS across the UK in a variety of different settings. **4. Lundbeck is supporting the development of services and online**	Comments noted. No action required. Comments noted. No action required.

Consultee	Comment	Response
	psychosocial support offerings. • To facilitate the introduction of appropriate psychosocial support, Lundbeck has launched an online psychosocial support tool, which is free of charge to the NHS and is available at: www.reduceyourdrinking.com. Lundbeck has also supported the development of a Psychosocial Support Booklet provided as a service to medicine, for use by healthcare professionals that are less experienced in delivering structured psychosocial support to a patient with mild alcohol dependence	
National Substance Misuse Non-Medical Prescribers Forum	The Forum recognises the significant change that the licensing of nalmefene may open up in the treatment of individuals drinking at hazardous/harmful levels. It brings a pharmaceutical arm to a harm reduction approach for alcohol in respect of the treatment of patients who are not physically dependant and this is welcome indeed. • Along with our comments we have attached two papers which we think the Appraisal Committee should consider- firstly "**Nalmefene for Alcohol Dependency"** in the *Drugs & Therapeutic Bulletin of the British Medical Journal* Vol 52 | No 5| May 2014. This concludes that "Based on the limitations of the evidence, the relatively modest reductions in drinking compared with placebo, lack of evidence on health related outcomes and concerns over the generalisability of the data, we cannot recommend the use of nalmefene."	Comment noted. Comments noted. As part of the appraisal process NICE sends the Appraisal Committee members the full text of the comments from the consultees and commentators and a summary of any comments received from other people or organisation. As a result of copy right law, NICE is unable to send Appraisal Committee members the actual attached papers. Nalmefene is recommended within its marketing authorisation, as an option for reducing alcohol consumption, for people with alcohol dependence who have a high drinking risk level (defined as alcohol consumption of more than 60 g/day for men and more than 40 g/day for women, according to the World Health Organization's drinking risk levels) without physical withdrawal symptoms, and who do not require immediate detoxification. See FAD section 1.1 The Committee concluded that nalmefene plus BRENDA reduces the number of heavy drinking days and total alcohol consumption compared with BRENDA alone, although the exact magnitude of effect was uncertain because of the post hoc subgroup analyses and the trials were not powered

Consultee	Comment	Response
		for these analyses. The Committee agreed that the EQ-5D data showed that nalmefene plus BRENDA improved health-related quality of life compared with placebo plus BRENDA. See FAD sections 4.6 and 4.8
	• The paper also contrasts the cost of nalmefene versus naltrexone – in effect double the cost of naltrexone.	Comment noted. The Committee noted that there were no trials directly comparing nalmefene plus psychosocial support with naltrexone plus psychosocial intervention, and the manufacturer had not presented an indirect comparison of the 2 treatments. The Committee agreed that the relative effectiveness of nalmefene plus psychosocial support and naltrexone plus psychosocial intervention was uncertain, mainly because of limitations in the available evidence base for naltrexone in people with mild alcohol dependence. The Committee had heard from the clinical specialists that naltrexone plus psychosocial intervention was not part of established practice for the reduction of alcohol consumption, and it agreed that naltrexone plus psychosocial intervention could not be considered an appropriate comparator. The Committee concluded that it would not consider further the comparison of nalmefene plus psychosocial support compared with naltrexone plus psychosocial intervention in its decision making. See FAD section 4.7
	• It also goes on to highlight the inconsistency of psychosocial interventions in the treatment of alcohol misuse in England notably within Primary Care [The marketing authorisation for nalmefene specifies that it should only be prescribed in conjunction with continuous psychosocial support focused on treatment adherence and reducing alcohol consumption] — which is the setting where the	Comment noted. The Committee was aware that the provision of psychosocial intervention differs throughout England. See FAD section 4.14

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	use of nalmefene would appear to be most relevant. These inconsistencies point to a lack of suitably trained staff across the country and this is linked to the different health infrastructures in place as well as differing health resource allocation between areas. The Forum is aware of examples of nalmefene being prescribed by specialist alcohol agencies [secondary care] – so as to be able to ensure the correct level of psychosocial support to patients.	
	• Secondly **"Evidence about the use of naltrexone and for different ways of using it in the treatment of alcoholism"** *John David Sinclair – Alcohol & Alcoholism Vol 36 No1, pp2-10 2001.* His paper details 8 double-blind placebo controlled studies using naltrexone in patients who were still drinking. Various psychosocial approaches were utilised in the studies. We would direct you to his "General Conclusions and Comments" on pp8.	Comment noted. As part of the appraisal process NICE sends the Appraisal Committee members the full text of the comments from the consultees and commentators and a summary of any comments received from other people or organisations.
	The Forum makes the following comments	Comment noted.
	• There appear to be no head to head trials of nalmefene v naltrexone to compare and contrast. This is something that we would like to see carried out.	Comment noted.
	• Previous contributors to this STA have made comment of nalmefene having less side effects and possibly less liver toxic than naltrexone. Given that they are almost identical agents the evidence for those differences appears limited. Nalmefene is licensed for use on an as needed basis: patients should take one tablet on days on which they perceive a risk of drinking – naltrexone could be given in the same way and therefore the risk of liver damage would appear in both cases to be very low. It is also worth noting that the hepatoxic effect of heavy drinking is much worse than either naltrexone or nalmefene.	Comments noted. The Committee noted that there were no trials directly comparing nalmefene plus psychosocial support with naltrexone plus psychosocial intervention, and the manufacturer had not presented an indirect comparison of the 2 treatments. The Committee agreed that the relative effectiveness of nalmefene plus psychosocial support and naltrexone plus psychosocial intervention was uncertain, mainly because of limitations in the available evidence base for naltrexone in people with mild alcohol dependence. The Committee had heard from the clinical specialists that naltrexone plus psychosocial intervention was not part of established practice for the reduction of alcohol consumption, and it agreed

Consultee	Comment	Response
		that naltrexone plus psychosocial intervention could not be considered an appropriate comparator. The Committee concluded that it would not consider further the comparison of nalmefene plus psychosocial support compared with naltrexone plus psychosocial intervention in its decision making. See FAD section 4.
	• The Forum would like to ask is there a role for naltrexone being prescribed to patients currently drinking [off-licence indication] in combination with psychosocial support? Would the Appraisal Committee be willing to comment on this?	Comment noted. The remit referred to NICE by the Department of Health is to appraise nalmefene within its licensed indication for reducing alcohol consumption in people with alcohol dependence. As naltrexone was not included in the remit, the Appraisal Committee is unable to make any recommendations on the use of naltrexone as a treatment for this patient group. Furthermore the Committee heard from the clinical specialists that naltrexone plus psychosocial intervention was not part of established practice for the reduction of alcohol consumption. See FAD Section 4.7
	Cost effectiveness – it is clear that naltrexone which can be prescribed as a generic pharmaceutical product in the United Kingdom has significant savings over nalmefene. This is another consideration that the committee may wish to comment on	Comment noted. The Committee was not presented with any evidence on the cost effectiveness of naltrexone.
Department of Health	"Taking each question in turn posed in the consultation documentation:	
	1. It does appear the relevant research evidence available for the use of nalmefene 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).	Comment noted. Please see the more detailed response to point 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.	Comment noted. Please see the more detailed response below

Consultee	Comment	Response
	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 nalmefene? 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	Comment noted. The Committee noted from the trials that patients must be diagnosed as having alcohol dependency using the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR), with an average daily alcohol consumption of medium risk or higher (more than 40 g [5 units] per day for men and more than 20 g [2.5 units] per day for women), at least 6 heavy drinking days (defined as more than 60 g per day for men and more than 40 g per day for women) in the preceding 28 days and equal or less than 14 abstinent days in the 4 weeks before the screening visit. See FAD section 4.4

Consultee	Comment	Response
	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 nalmefene 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 nalmefene, 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.	Comments noted. Consultation comments were received from the Royal College of GPs, the Royal College of Physicians and a number of NHS professionals. There were also 3 GPs on the Committee involved in the appraisal. See sections 9.1 and 10 of the FAD
	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.	Comment noted. The Committee noted from the trials that patients must be diagnosed as having alcohol dependency using the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR), with an average daily alcohol consumption of medium risk or higher (more than 40 g [5 units] per day for men and more than 20 g [2.5 units] per day for women), at least 6 heavy drinking days (defined as more than 60 g per day for men and more than 40 g per day for women) in the preceding 28 days

Consultee	Comment	Response
		and equal or less than 14 abstinent days in the 4 weeks before the screening visit. See FAD section 4.4
	4. We do not have any additional suggestions to make concerning the lack of any specific considerations identified to ensure avoidance of unlawful discrimination.	Comment noted. No action required
	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.	Comments noted. NICE's Guidance Executive considered the specific circumstances for which it would be appropriate to extend the standard 3 month funding period for relevant health authorities to comply with the recommendations. The Guidance Executive decided that the circumstances were not sufficiently met, and therefore the 3-month funding period was appropriate.
		Comment noted. Consultation comments were received from a number of professional and patient/carer groups. See FAD section 10
	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).	NICE's Guidance Executive considered the specific circumstances for which it would be appropriate to extend the standard 3 month funding period for relevant health authorities to comply with the recommendations. The Guidance Executive decided that the circumstances were not sufficiently met, and therefore the 3-month funding period was appropriate. See FAD sections 4.14 and 5.1.
		Comment noted. The Committee noted the uncertainty and conflicting opinions among the stakeholders regarding the most appropriate setting for prescribing nalmefene and psychosocial support. However the Committee was aware that

Consultee	Comment	Response
		making specific recommendations about the setting for prescribing nalmefene was outside the scope of a technology appraisal. See FAD section 4.3
	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.	Comments noted. NICE's Guidance Executive considered the specific circumstances for which it would be appropriate to extend the standard 3 month funding period for relevant health authorities to comply with the recommendations. The Guidance Executive decided that the circumstances were not sufficiently met, and therefore the 3-month funding period was appropriate. See FAD section 5.1
	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.	Comments noted. NICE's Guidance Executive considered the specific circumstances for which it would be appropriate to extend the standard 3 month funding period for relevant health authorities to comply with the recommendations. The Guidance Executive decided that the circumstances were not sufficiently met, and therefore the 3-month funding period was appropriate. See FAD section 5.1
	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).	Comment noted. The diagnosis of alcohol dependence is outside the scope of this technology appraisal. However, the Committee noted that in clinical practice, most patients with mild alcohol dependency (defined using an assessment tool such as the alcohol use disorders identification kit [AUDIT]) would be treated in the primary care setting with delivery of brief or extended brief interventions, and may not see a secondary care specialist. The Committee noted from the trials that patients must be diagnosed as having alcohol

Consultee	Comment	Response
	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...)".	dependency using the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR), with an average daily alcohol consumption of medium or higher risk (60g per day or greater [7.5 units per day or greater] for men and 40g/day or greater [5 units per day or greater] for women), at least 6 heavy drinking days in the preceding 28 days and equal or less than 14 abstinent days in the 4 weeks before the screening visit. See FAD section 4.4
NHS Stafford and Surrounds CCG	Many thanks for the information provided, which was thoroughly comprehensive in terms of clinical efficacy, adverse effects and cost effectiveness. All of which I think are sufficiently robust to support the recommendations made in the ACD. East Staffordshire, South East Staffs & Seisdon Peninsular and Stafford and Surrounds CCGs. I'm more concerned about what the ACD doesn't cover and around implementation and delivery of the recommendations. Comments as follows:- My understanding is that commissioning of alcohol services is the responsibility of local authorities; I think this is the first TA that will be their responsibility to implement. The infrastructure arrangements therefore are potentially quite complex as CCGs will seek to recharge prescribing costs (by GPs) to local authorities and arrangements need to be made to facilitate this. CCGs are unlikely to support funding of a service for which they do not have commissioning responsibility, so this is potentially important. Given that this is a novel drug, the question is really what the patient pathway	Comment noted. No action required. Comment noted. Comments noted. NICE's Guidance Executive considered the specific circumstances for which it would be appropriate to extend the standard 3 month funding period for relevant health authorities to comply with the recommendations. The Guidance Executive decided that the circumstances were not sufficiently met, and therefore the 3-month funding period was appropriate. Comment noted. The Committee noted the uncertainty and conflicting opinions among the stakeholders regarding the most appropriate setting for prescribing nalmefene in conjunction with psychosocial support. However the Committee was aware that making specific recommendations about the setting for prescribing nalmefene was outside

Consultee	Comment	Response
	should like. My thinking is that services providing psychosocial support which are probably the mainstay of alcohol services will not have access to prescribers qualified to prescribe this drug. Is it therefore in the intention that such services enter into "shared care" with GPs to treat these patients.	the scope of a technology appraisal. See FAD section 4.3 Comment noted. Please see response above
	This adds another layer of complexity as the entering into a shared care agreement is a voluntary agreement and not something enshrined within the GMS/PMS contract, which may not therefore provide the level of assurance that would be needed.	Comment noted. Please see response above
	Another option would be for LA's to commission a service from GPs which might include nalmefene prescribing and monitoring, the SPC advises on a monthly review around the need to continue, which could cause capacity issues. My sense would be that the service specification for this option would need to be comprehensive in terms of starting and continuation criteria and a clear steer on maximum duration of treatment.	Comment noted. Please see response above. Comment noted. No action required.
	LA's will need to be assured that GPs aren't prescribing this agent without the appropriate psychosocial support, nor will they be keen to pay for use outside of a commissioned service.	Comments noted. Consultation comments were requested from the Association of Directors of Public Health as well as from a number of other commissioning organisations. See FAD section 10.
	So in summary, I'm happy with the ACD recommendation, but think there may be more work to do in terms of how this new agent will fit into pathways and processes.	
	Have any LA commissioners been involved in the appraisal?	NICE has produced an 'alcohol-use disorder pathway (2013) which may be up-dated with the recommendations for this appraisal if considered appropriate. See FAD section 6.
	Is it intended that a pathway proposal might be published alongside the TA?	Comments noted. NICE's Guidance Executive considered the specific circumstances for which it would be appropriate to extend the standard 3 month funding period for relevant health authorities to comply with the recommendations. The Guidance Executive decided that the circumstances were not sufficiently met, and therefore the 3-month
	Without some comprehensive implementation tools and guidance, I suspect this	

Consultee	Comment	Response
	may need longer than 90 days to get in place.	funding period was appropriate.
Royal College of Physicians	I write on behalf of [redacted], RCP registrar with regard for your request for comments on the above ACD. As nalmefene is specifically used for the treatment of alcohol dependence the RCP would defer to the opinion of the Royal College of Psychiatrists and its Faculty of Addiction in these matters. As such, we will not be submitting additional comment on this occasion.	Comment noted. No action required.

The Royal College of Nursing had no comments

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
Royal College of Psychiatrists	Thank you for the opportunity to comment on the ACM for nalmefene on behalf of the Royal College of Psychiatrists	Comment noted.
	Having read the ACM in my opinion all the relevant information has been taken into account and the summaries of that evidence in relation to clinical and cost effectiveness are reasonable	Comment noted. No action required.
	I agree with the recommendations and believe they are reasonable to go forward as guidance for the NHS	Comment noted. Nalmefene is recommended within its marketing authorisation, as an option for reducing alcohol consumption, for people with alcohol dependence who have a high drinking risk level (defined as alcohol consumption of more than 60 g/day for men and more than 40 g/day for women, according to the World Health Organization's drinking risk levels) without physical withdrawal symptoms, and who do not require immediate detoxification. See FAD section 1.1
	I do not see any issues which should lead to an extension of the date and therefore the standard time period should apply	Comments noted. NICE's Guidance Executive considered the specific circumstances for which it would be appropriate to extend the standard 3 month funding period for relevant health authorities to comply with the recommendations. The Guidance Executive decided that the circumstances were not sufficiently met, and therefore the 3-month funding period was appropriate.

Nominating organisation	Comment	Response
	Comments on the ACD **3.38** review of Analysis 2 I would question the assumption that there is a need for 50% of patients to receive outpatient medically assisted withdrawal. The inclusion criteria for these studies was those patients without physical withdrawals therefore unless the assumption is increasing severity of withdrawals to a level where they would require a medically assisted withdrawal. **4.10** with regard to length of treatment in the model being 12/12 it is important to note that the usual length of extended brief intervention is 6-12 weeks and is usually completed within 3 months not 12. There may be opportunities for subsequent booster sessions but in clinical practice the duration of this PSI would be less than 12 months I do not feel either of these comments alters the recommendations and conclusions of the ACM	Comment noted. Comment noted. The Committee was aware for heavy drinking mild alcohol dependency, NICE clinical guideline 115 recommended that psychosocial intervention (including behavioural therapies, cognitive behavioural therapy and behavioural couples therapies) should typically consist of 1 hour weekly sessions over a 12 week period. See FAD section 4.3
Royal College of General Practitioners	Nalmefene is a relatively old drug and similar, but sufficiently different to Naltrexone to justify separate appraisal. Naltrexone is not licensed for controlled reduction, but recommended by NICE CG115 for this indication. The use of Naltrexone instead of Nalmefene “PRN” is also known as the “Sinclair method” Ref: Sinclair, John David (June 2001). Targeted Use of Naltrexone Without Prior Detoxification in the Treatment of Alcohol Dependence: A Factorial Double-Blind, Placebo-Controlled Trial". Journal of Clinical Pharmacology (Oxford Journal of Medicine) 21 (3): 287–292. PMID 11386491; Sinclair, J.D. (January 14, 2000). "Evidence about the use of naltrexone and for different ways of using it in the treatment of alcoholism". Alcohol and Alcoholism (Oxford Journal of Medicine) 36 (1): 2–10. doi:10.1093/alcalc/36.1.2. PMID 11139409. There is considerable confusion with regards to the definition of alcohol use disorders, worsened by relatively recent tries to make the terms used more	Comment noted. No action required Comment noted. No action required Comment noted. No action required.

Nominating organisation	Comment	Response
	acceptable to the public and patients.	
	The RCGP Substance Misuse Unit is recommending the use of the following terms, which are compatible with NICE CG115: Low risk drinking Hazardous drinking Harmful drinking	Comment noted. No action required.
	In the RCGP Certificate in the Management of Alcohol Problems in Primary Care, which has trained over 3000 GPs and other healthcare professionals, we describe dependence as a subform of harmful drinking, therefore all dependent drinkers are also harmful, but not all harmful drinkers would be seen as dependent.	Comment noted. No action required.
	Assessing the severity of alcohol dependence is important as it has direct consequences for patients and treatment choices. Mild dependency does not require the same treatment as moderate or severe dependency.	Comment noted. No action required
	There is evidence that not everybody who drinks levels of alcohol that would usually result in developing physical dependence and therefore alcohol withdrawal syndrome (AWS, typically above 15-20 units) will develop AWS (Ref: Absence of alcohol withdrawal syndrome in a remote Indigenous community; Stephen A Margolis, Valmae A Ypinazar, Alan R Clough and Ernest Hunter; Med J Aust 2008; 189 (10): 596.).	Comment noted. No action required
	The treatment for mild dependence and harmful drinking in the absence of elements of dependence is possibly very similar and often described as “extended brief intervention”, which is a conundrum derived from the term Brief Intervention which is used for hazardous drinking. As there is no standard definition of what a brief intervention entails, there is no definite agreement what an extended brief intervention should exactly look like. We therefore recommend the use of the term “Brief Treatment” for harmful drinking, which we suggest entails of a small number of sessions which are delivered by an appropriately trained individual.	Comment noted.
	Another complication is that in order to diagnose alcohol dependence,	

Nominating organisation	Comment	Response
	clinicians and other healthcare professionals must be appropriately trained; the use of assessment tools like AUDIT, SADQ or LDQ can aid decision making, however the more significant (or severe) the diagnosis is, the more important it is to ensure the person making the diagnosis to be competent in the assessment. As this is a clinical decision, we recommend taking a full history as part of a clinical interview and also cover areas like sleep duration, the use of "eye openers" (consuming alcohol in the morning), withdrawal symptoms, overall units consumed, blood test results and the use of a breathalyser. It is at the discretion of the clinician how much information is required to come to a preliminary or definite diagnosis. **AUDIT / SADQ / Sleep duration / Eye opener / With-drawal / Units/day** Harmful: 16+ / <3 / Normal / - / - / <15 Dependence Mild: 16+ / <15 / 8+ hrs / - / + / <15 Moderate: 20+ / 15-30 / 6-8 hrs / + / ++ / 15-30 Severe: 20+ / 30+ / 4-6 hrs / ++ / +++ / 30+ Reference: RCGP Certificate in the Management of Alcohol Problems in Primary Care	Comment noted. The diagnosis of alcohol dependence is outside the scope of this technology appraisal but is detailed in the NICE alcohol-use disorder pathway (2013). The Committee noted from the trials that patients must be diagnosed as having alcohol dependency using the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR), with an average daily alcohol consumption of medium risk or higher (more than 40 g [5 units] per day for men and more than 20 g [2.5 units] per day for women), at least 6 heavy drinking days (defined as more than 60 g per day for men and more than 40 g per day for women) in the preceding 28 days and equal or less than 14 abstinent days in the 4 weeks before the screening visit. See FAD section 4.4
	We recognise that alcohol treatment is highly variable and service provision is patchy throughout England; alcohol treatment services might or might not be commissioned according to NICE clinical, public health or commissioning guidelines and there is a lack, often complete absence, of clinical advisors in public health England and local authority who can ensure that clinical treatment is commissioned safely. For example, NICE published guidelines on how to commission alcohol services (CMG38 "Services for the identification and treatment of hazardous drinking, harmful drinking and alcohol dependence in children, young people and adults"), but is possibly	Comment noted. The Committee noted that the provision of psychosocial intervention differs throughout England and as the license for nalmefene mandates the treatment can only be given to patients in combination with psychosocial intervention the relevant health bodies should be provided with sufficient time to organise the service. NICE's Guidance Executive considered the specific circumstances for which it would be appropriate to

Nominating organisation	Comment	Response
	not used by commissioners.	extend the standard 3 month funding period for relevant health authorities to comply with the recommendations. The Guidance Executive decided that the circumstances were not sufficiently met, and therefore the 3-month funding period was appropriate.
	It is likely that the majority of individuals should address their alcohol intake in a structured treatment that is not hazardous to drinkers who can be given a brief intervention, and who are either harmful or mildly dependent. The Adult Psychiatric Morbidity Survey 2007 gives a prevalence for alcohol dependence in England at 5.9%, of which the vast majority are mildly dependent (5.4% of the population). Only 0.5% of the population are either moderately or severely dependent.	Comment noted. No action required.
	If the case mix of a well-commissioned community alcohol service is offering appropriate treatment for all service users, it can be assumed that up to 90% of service user are mildly dependent and require a short treatment with or without pharmacotherapy, as currently recommended by NICE.	Comment noted. No action required.
	The typical GP (assuming 40-50 patient contacts per day) would encounter at least 2 alcohol dependent patients, who would be likely to be mildly dependent and suitable for treatment. This does not take into account the higher risk of both mental and physical health complications in harmful drinkers, which is again likely to increase presentation frequency for comorbidities.	Comment noted. No action required.
	Whilst NICE recommends structured psychosocial interventions (PSI) as first line treatment for alcohol use disorders, it also acknowledges the role of pharmacotherapy as an additional treatment option if PSI alone is insufficient or if a service user requests it specifically. CMG38 recommends assuming that 30% of service users will require pharmacotherapy, but does not detail what budget should be set aside.	Comment noted. No action required.
	There is overwhelming evidence that addiction is a brain disease (Leshner AI. Science. 2007;278:45-7, National Institute on Drug Abuse. 2010. http://www.drugabuse.gov/publications/science-addiction), like depression	Comment noted. No action required.

Nominating organisation	Comment	Response
	or Parkinson's disease. Both psychosocial interventions (PSI) and pharmacotherapy are suitable treatment modalities and highly effective for some addictions, whilst others are less responsive.	
	The initial identification, assessment and treatment of alcohol use disorders is something all GPs are confronted with, however competence is difficult to assess. Addiction to alcohol is often seen as a failure or weakness of character rather than a treatable condition.	Comment noted. No action required.
	Most GPs would require additional training to clinically assess alcohol use disorder, including making the right diagnosis with regards to severity of dependence. The RCGP is confident that the RCGP Certificate in the Management of Alcohol Problems in Primary Care fulfils this as a minimum standard. As psychosocial interventions (PSI) are often delivered by other healthcare professionals like nurses or key workers (qualified according to DANOS – drugs and alcohol national occupational standards), it is safe to presume that treatment will only be delivered as part of a shared care scheme. The idea that GPs would treat alcohol dependence independently is unlikely. PSIs should be available according to NICE CG115 as a minimum.	Comment noted. The Committee noted the uncertainty and conflicting opinions among the stakeholders regarding the most appropriate setting for prescribing nalmefene and psychosocial support. The Committee accepted that BRENDA, as described in the 3 nalmefene studies, closely resembled current established care practice. However the Committee was aware that making specific recommendations about the setting for prescribing nalmefene was outside the scope of a technology appraisal. See FAD section 4.3 and 4.5.
	• Has all of the relevant evidence been taken into account? The evidence review group appear to have considered the relevant and available evidence and importantly highlighted areas where the evidence is lacking or not provided by the manufacturer	Comment noted. No action required.
	• Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Yes	Comment noted. No action required.
	• Are the provisional recommendations sound and a suitable basis for guidance to the NHS? (Please comment on the generalisability of the trial populations to clinical practice and whether this patient population could be easily identified) There does appear to be concerns around the generalisabilty of the	Comment noted. The Committee concluded that the baseline characteristics of the populations in the 3

Nominating organisation	Comment	Response
	population -in particular patients in primary care suffer from multimorbidity and polypharmacy and this must be considered in clinic trials	studies were not wholly generalisable to clinical practice in England, but provided sufficient evidence to allow clinicians to determine the patient population for treatment with nalmefene and psychosocial support. See FAD section 4.4
	• Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? The scope of the guidelines must take this into account and the equality assessment report suggests this.	Comment noted. The Committee concluded that its recommendation on the use of nalmefene plus psychosocial support does not have a particular impact on any group with a protected characteristic in the equality legislation and that there was no need to alter or add to its recommendations. See FAD section 4.15
	• Given the requirement for relevant health bodies (clinical commissioning groups, NHS England and local authorities) to provide funding to ensure that the health technology is available within 3 months, from the date the recommendation is published by NICE (see section 5.1), is an extension to this normal period appropriate because any of the following circumstances apply: I don't think so ○ The health technology cannot be appropriately administered until training is in place? ○ The health technology cannot be appropriately administered until certain health service infrastructure requirements including goods, materials or other facilities are in place? ○ The health technology cannot be appropriately administered until other appropriate health services resources, including staff, are in place? If so, please specify the reasons and an estimate of the time period within	Comments noted. NICE's Guidance Executive considered the specific circumstances for which it would be appropriate to extend the standard 3 month funding period for relevant health authorities to comply with the recommendations. The Guidance Executive decided that the circumstances were not sufficiently met, and therefore the 3-month funding period was appropriate.

Nominating organisation	Comment	Response
	which the recommendation can be complied with.	

Comments received from commentators

Commentator	Comment	Response
Institute Of Alcohol Studies	The Comments IAS Wishes to submit to this stage of the STA Appraisal consultation are in addition to those made in our submission to NICE In July 2013. Based on our reading of the appraisal consultation documents we note the following: 1. No Guidance is provided on the identification of 'patients with mild dependence not requiring detoxification'. The nalmefene studies considered in the STA were undertaken in this specific population and there is no evidence to support use of this medication in other populations of drinkers. Without specific guidance on patient eligibility there is a very real danger that the medication could be used to treat any patients who presents with a drinking problem. Any recommendation made by NICE should contain specific eligibility criteria for patient selection e.g. AUDIT Scores etc. 2. Insufficient attention has been paid to the concerns raised by the Expert Review Group In relation to the duration of treatment. While it is highly unlikely that a GP would continue to prescribe nalmefene for patients who continue to drink heavily, no specific guidance is provided about the duration of treatment. Without this it is possible that some patients might continue to receive nalmefene inappropriately when they should instead be reassessed and referred to secondary care.	Comment noted. The diagnosis of alcohol dependence is outside the scope of this appraisal but is detailed in the NICE alcohol-use disorder pathway (2013) and in FAD section 4.3. The Committee noted from the trials that patients must be diagnosed as having alcohol dependency using the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR), with an average daily alcohol consumption classed as medium risk or higher (more than 40 g [5 units] per day for men and more than 20 g [2.5 units] per day for women) with at least 6 heavy drinking days (defined as more than 60 g per day for men and more than 40 g per day for women) in the preceding 28 days and equal or less than 14 abstinent days in the 4 weeks before the screening visit. See FAD section 4.4 Comment noted. The Committee understood that the length of treatment time would be decided on an individual basis between the clinician and patient but that 12 months of treatment was possible. See FAD section 4.11
Association of Directors of Public Health	In response to your specific questions I have the following comments. As this medication is likely to be used in primary care and the costs of the drugs are likely to sit within the primary care prescribing budget – this cost is	Comment noted. The Committee noted the uncertainty and conflicting opinions among the

Commentator	Comment	Response
	likely to come from NHS commissioning budgets as historically with primary care prescribing it has been very hard to disentangle 'public health defined prescribing in primary care' from other NHS prescribing. With regards to the Psychosocial support for alcohol dependency – this is already commissioned by Local Authority public health. In conclusion I see no reason why local areas can't comply with the recommendations in this appraisal within 3 months of its publication.	stakeholders regarding the most appropriate setting for prescribing nalmefene and psychosocial support. However the Committee was aware that making specific recommendations about the setting for prescribing nalmefene was outside the scope of a technology appraisal. See FAD section 4.3 Comment noted. The Committee noted that the provision of psychosocial intervention differs throughout England and as the license for nalmefene mandates the treatment can only be given to patients in combination with psychosocial intervention the relevant health bodies should be provided with sufficient time to organise the service. NICE's Guidance Executive considered the specific circumstances for which it would be appropriate to extend the standard 3 month funding period for relevant health authorities to comply with the recommendations. The Guidance Executive decided that the circumstances were not sufficiently met, and therefore the 3-month funding period was appropriate.

Comments received from members of the public

Role*	Section	Comment	Response
NHS Professional 1	Conflicts	No	
	Comments on ACD	The first comment relates to the need for "continuous psychosocial support focused on treatment adherence and reducing alcohol consumption", which is part of the marketing authorisation. In practice this may be difficult to achieve and this may depend on whether the	Comment noted. The Committee noted the uncertainty and conflicting opinions among the stakeholders regarding the most appropriate setting for prescribing nalmefene and psychosocial

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patient', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Section	Comment	Response
		drug is intended to be used in a primary care (GP) setting or is intended to be prescribed in a specialist setting, where psychosocial support may be more readily available. It is difficult to see therefore how the drug could be used in a GP setting. It would be useful if NICE is able to comment and provide a steer on this within the TA. The second comment relates to commissioning responsibility for alcohol services. This now sits with Local Authorities / Public Health, rather than with CCGs, so presumably this should also be made clear within the TA. The 3 month timescale for implementation might need to be extended if commissioners have to develop psychosocial support services - if these are not already provided.	support. However the Committee was aware that making specific recommendations about the setting for prescribing nalmefene was outside the scope of a technology appraisal. See FAD section 4.3. Comment noted. NICE's Guidance Executive considered the specific circumstances for which it would be appropriate to extend the standard 3 month funding period for relevant health authorities to comply with the recommendations. The Guidance Executive decided that the circumstances were not sufficiently met, and therefore the 3-month funding period was appropriate. Comment noted. Please see response above.
NHS Professional 2	Conflicts	No	
	Comments on ACD	The document does not comment on the lack of testing of the integrity of the double-blind in the 2 studies by Mann et al and by Gual et al. This is critical, because the treatment response in both studies was small in comparison to the size of the placebo response, and the difference could be due to assessor or participant bias, for which there is huge potential given that retrospective accounts of drinking are the basis of the main outcome measures, and such bias could have been possible through guessing who was on nalmefene, perhaps through presence of side effects. That both studies seem to have been sponsored by Lundbeck should add to this concern.	Comment noted. The Committee for Medical Products for Human Use (CHMP) assessment report considered that the pivotal 6-month placebo-controlled trials were all double-blind in study design. All participants were blinded to outcomes. The method for sequence generation in the randomisation process and the allocation concealment were adequate. The Committee was concerned that the differences between the treatment groups were relatively small (13% in heavy drinking days and 11% in total alcohol consumption), suggesting that most of the treatment gain from nalmefene could be attributed

Role*	Section	Comment	Response
			to the psychosocial support (BRENDA). See FAD section 4.6
		The document seems to accept the Lundbeck version of nalmefene's mode of action in reducing drinking. I would be interested to know if participants most affected by nausea drank less. Is it actually an aversive agent? If it works by reducing reward, is this not a pharmacologically induced equivalent to tolerance and isn't tolerance often cited as reason for escalation, not for reduction.	Comment noted. The Committee for Medical Products for Human Use (CHMP) assessment report for nalmefene which was provided by the European Medicines Authority takes account of the mode of action of nalmefene. See FAD section 2.1
		As an opioid receptor antagonist, nalmefene cannot be expected to have effects specific to drinking behaviour. If it impacts on drinking, it impacts on all rewarding behaviour and thereby, may have very pervasive negative effects in areas such as exercise, hobbies and interests, and, of course, relationships, generally, and sex, perhaps especially.	Comment noted. Please see response above.
		The document fails to address the psychology of taking a tablet to reduce drinking. In the real world, as opposed to trials, would some people on nalmefene be less interested in psychosocial interventions, purely because they had their tablet to take? Would some people, for anticipating having a drink and taking a tablet, then feel it must be a drinking day because I've taken my tablet, i.e. the tablet could actually increase the probability of some alcohol being consumed? In this respect it is noteworthy that nalmefene per se, is not being promoted as causing more alcohol free days. Could some people think that for not having yet taken a tablet, today must be a binge? These possibilities are based on sound principles of conditioning and expectation.	Comment noted. The Committee heard from clinical specialists that although some patients in clinical practice may be less likely to adhere to treatment because of the need to document their drinking level, or to attend their scheduled psychosocial support sessions, there are many who would be sufficiently motivated to adhere to all aspects of the treatment. See FAD section 4.13
		The document fails to adequately emphasise the high dropout rates in the 2 main studies of nalmefene. I doubt that prescribed nalmefene will be taken at all regularly by most who receive it and in primary care, a psychosocial element to treatment will be offered rarely, and taken up, at best, only as it would have in the absence of the medication. The potential for widespread implementation of psychosocial treatments to reduce alcohol related harm is huge, but it isn't going to happen	Comment noted. The marketing authorisation states that nalmefene should only be prescribed in conjunction with continuous psychosocial support focused on treatment adherence and reducing alcohol consumption, and be initiated only in patients who continue to have a high drinking risk

Role*	Section	Comment	Response
		because of nalmefene. Given that subgroup analysis of study participants who continued to drink at high risk level, not just medium risk level, produced the more favourable results for nalmefene; why not advocate it for people drinking at very high risk level; especially if they have already had detoxifications and returned to such heavy drinking? The history of 'alcoholism' as a useful cultural concept and the consequent controversies over 'controlled' drinking explain why Lundbeck steered clear of these drinkers. Clearly, the potential for reduction from huge levels of consumption is also huge. After 40 years of having nalmefene, and after who knows how many trial flops (how many of these on drinkers?), Lundbeck has concocted a commercial use for nalmefene.	level 2 weeks after initial assessment. See FAD section 1.1 and comment above Comment noted. Guidance can only be developed in line with the marketing authorisation 'as an option for reducing alcohol consumption, for people with alcohol dependence who have a high drinking risk level (defined as alcohol consumption of more than 60 g/day for men and more than 40 g/day for women, according to the World Health Organization's drinking risk levels) without physical withdrawal symptoms, and who do not require immediate detoxification. See FAD section 1.1
Healthcare other	Conflicts	No	
	Comments on ACD	Turning Point is a leading health and social care organisation working in over 200 locations across England and Wales. We have been operating for 50 years, providing specialist and integrated services that meet the needs of individuals, families and communities. We are a social enterprise reinvesting its surplus to provide the best services in the right locations for those that need them most across mental health, learning disability, substance misuse, the criminal justice, primary care and employment. Turning Point welcomes the opportunity to feed in to this consultation on the use of nalmefene for reducing alcohol consumption in people with alcohol dependence. Feedback to the consultation questions has been gathered by Turning Point's Clinical Management team and responses are set out below. The key points from our response are: • Not all evidence related to the use of naltrexone has been taken into account. • There are issues related to the level of complexity of psychosocial interventions needed in the client group for which nalmefene has the marketing authorisation • There are no issues related to discrimination against certain groups. • We do not foresee issues with ability to offer nalmefene within the	Comment noted. No action required. Comment noted. No action required.

Role*	Section	Comment	Response
		normal three month timescale after NICE recommendation. Question 1: Has all of the relevant evidence been taken into account? We have identified that there is relevant evidence that has not been taken into account. The first is that there has been a lack of economic comparison with the medication naltrexone. The second aspect of evidence that is lacking is related to recovery capital and the complexity of the psychosocial interventions required for the client group for which nalmefene has marketing authorisation.	Comment noted. The Committee was aware that it had heard from the clinical specialists that naltrexone plus psychosocial intervention was not part of established practice for the reduction of alcohol consumption and the Committee agreed that naltrexone plus psychosocial intervention could not be considered an appropriate comparator. The Committee concluded that it would not consider further the comparison of nalmefene plus psychosocial support compared with naltrexone plus psychosocial intervention in its decision making. See FAD sections 4.2 and 4.7
		The Committee identified that naltrexone plus psychosocial intervention was not an appropriate comparator to nalmefene as it was not part of the established treatment for the reduction of alcohol consumption. We believe that there is a need for economic modelling of naltrexone and a comparison to nalmefene. The reasons for this are identified below: • Regarding the issue of naltrexone not being an established treatment in England (para 4.6), it is important to understand that the reason why services typically have difficulty providing this level of treatment (para 4.1) is because services for non-dependent drinkers are not currently funded by the NHS such clients are signposted by the NHS to non-statutory and voluntary, community and social enterprise (VCSE) sector services for brief interventions only. This is despite evidence that this group benefit from reduced alcohol consumption as reducing high risk drinking reduces the morbidity of numerous physical diseases. • We believe that Naltrexone is suitable to be used in comparison to nalmefene. The unlicensed use of Naltrexone for alcohol should be compared in an economic analysis to the licensed use of nalmefene. Naltrexone in dependent drinkers has a large evidence base, and paragraph 3.12 refers to three Randomised Control Trials	Comment noted. No action required Comment noted. The clinical specialists explained to the Committee that naltrexone is used in practice to treat a different patient group than those included in the nalmefene trials, with abstinence as the treatment goal The Committee agreed that the relative effectiveness of nalmefene plus psychosocial support and naltrexone plus psychosocial intervention was uncertain, mainly because of limitations in the available evidence base for naltrexone in people with mild alcohol

Role*	Section	Comment	Response
		(RCTs) of naltrexone in alcohol dependence. There are also three studies of naltrexone used on an as needed basis similar to that for nalmefene, although these studies were not RCTs.	dependence. See FAD sections 4.2 and 4.7
		• The document quotes NICE clinical guideline 115 that oral naltrexone does not have UK marketing authorisation for this indication (for alcohol) (paragraphs 4.1 and 4.6). In fact there was a generic oral naltrexone which did have a marketing authorisation for alcohol post-detox licensed in the UK in March 2010 by Accord Healthcare (PL 20075/0144), which incidentally was prior to CG115 being issued in Feb 2011.	Comment noted. The Committee heard from the clinical specialists that naltrexone is used in practice to treat a different patient group than those included in the nalmefene trials, with abstinence as the treatment goal. See FAD section 4.2
		• Some services nationally have been using naltrexone to assist in the treatment of non-dependent drinkers. However specific funding for pharmacological interventions in those not having structured psychosocial interventions is not recognised either by the Commissioners of NHS services or by Public Health England. This is a problem for services, which therefore have to fund such Tier 2 medication interventions as added value in order to improve outcomes in this group. Commissioners have only recently identified that this non-dependent group as requiring psychosocial interventions, and have not as yet recognised that some of this group also may benefit from medication interventions such as nalmefene or naltrexone.	Comment noted.
		• Because naltrexone and nalmefene are so pharmacological similar, we disagree with the statement that naltrexone would be used in practice to treat a different patient group than those included in the nalmefene trials, with abstinence as the treatment goal. Due to funding issues within services, providers may choose to make use of medication outside of their license, based on the costing of the medication.	Comment noted. The Committee heard from the clinical specialists that naltrexone is used in practice to treat a different patient group than those included in the nalmefene trials, with abstinence as the treatment goal. See FAD section 4.2
		Question 1: Has all of the relevant evidence been taken into account? The second aspect of evidence that we believe is lacking is related to recovery capital and the complexity of psychosocial interventions required. There are a number of points related to this highlighted below: • Non-dependent drinkers typically have high recovery capital: nalmefene is targeted at high risk drinkers, rather than dependent	

Role*	Section	Comment	Response
		drinkers. This subgroup of drinkers have both less severe problems and a higher level of recovery capital (personal, social and community assets) than clients with alcohol dependence - who may have much lower levels of recovery capital and who may require treatment with medical and psychological interventions by addiction services. The reason that this is significant is because it helps determine the level of psychosocial intervention required. A high level of psychosocial intervention is typically required for more dependent drinkers or those with a lower level of recovery capital, whereas only a relatively low level of psychosocial intervention is required for non-dependent drinkers and those with a high level of recovery capital. The recovery research suggests that brief interventions or self-help interventions may be all that is required for those with high recovery capital. Hence low level support would be typical of physical health medications, such as periodic assessment of compliance, side-effects and efficacy may be all that is required. Computerised CBT as with www.reduceyourdrinking.com (12 sessions) and Breaking Free Online are likely to be sufficient for the majority of patients. The requirement for continuous psychosocial support focussed on treatment adherence and reducing alcohol consumption would I think be met by this, although it would be helpful to clarify this in the guidance.	Comment noted. The Committee heard from the clinical specialists that although BRENDA is not used in its entirety in clinical practice, most of the components within it are currently provided in the form of brief or extended brief interventions and could be administered by healthcare professionals. See FAD section 4.5
		• Amber vs Green traffic lighting where high recovery capital and no dependence means only a low level of psychosocial support is required: This means that the situation is very different from the current situation with naltrexone, acamprosate and disulfiram, which are used in alcohol dependence and rated as amber drugs that should be started by specialists (or specialist generalists), but which may be continued by any doctor including the GP. The reason these drugs are rated amber is because of the need for significant psychosocial support, because of the presence of the dependency syndrome. Now the situation with nalmefene is quite different because the population is quite different. Nalmefene only requires a low level of psychosocial support for its licenced indication, and can be taken as needed in this patient population, and therefore can be rated green i.e. it can be initiated by any doctor including GPs.	Comment noted. No action required
		• BRENDA as a complex psychosocial intervention for use in primary care: Although BRENDA was used in the industry funded studies,	

Role*	Section	Comment	Response
		which is a fairly intensive intervention to use in primary care, Nalmefene does not appear to require this level of intervention from the clinical point of view as explained above. Indeed such an intervention is likely to have reduced rather than increased the apparent medication effect of the nalmefene. Although the industry funded evidence base is only generalisable if BRENDA is used, BRENDA is highly likely to be unnecessary overkill for use in the NHS in general.	Comment noted. The Committee received comments from a patient and carer group during the consultation period suggesting that BRENDA could be of a greater intensity than would be required to accompany nalmefene where a treatment such as brief intervention could be sufficient. The Committee heard from the clinical specialists that although BRENDA is not used in its entirety in clinical practice, most of the components within it are currently provided in the form of brief or extended brief interventions and could be administered by healthcare professionals. See FAD sections 4.2 and 4.5
		Question 2: Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? YES, but what is missing is a cost-effectiveness comparison with naltrexone, and consideration of the non-licensed use of naltrexone.	Comment noted. The Committee noted that there were no trials directly comparing nalmefene plus psychosocial support with naltrexone plus psychosocial intervention. The Committee agreed that the relative effectiveness of nalmefene plus psychosocial support and naltrexone plus psychosocial intervention was uncertain due mainly to limitations in the available evidence base for naltrexone in people with mild alcohol dependence. The Committee concluded that it would not consider further the comparison of nalmefene plus psychosocial support compared with naltrexone plus psychosocial intervention in its decision making. See FAD section 4.7
		Question 3: Are the provisional recommendations sound and a suitable basis for guidance to the NHS? YES, but need to take account of the issues about naltrexone above. In a cost conscious NHS, we would tend to use a product outside its licensed indication first line if it is considerably cheaper, and use the	Comment noted. Please see response above

Role*	Section	Comment	Response
		more expensive product second line. Question 4: Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? NO Question 5: Given the requirement for relevant health bodies (clinical commissioning groups, NHS England and local authorities) to provide funding to ensure that the health technology is available within 3 months, from the date the recommendation is published by NICE (see section 5.1), is an extension to this normal period appropriate because any of the following circumstances apply: 5.1: The health technology cannot be appropriately administered until training is in place? • NO, as minimal training is required for prescribers and psychosocial interventions 5.2: The health technology cannot be appropriately administered until certain health service infrastructure requirements including goods, materials or other facilities are in place? • NO, as urine screening tests for opioids are available in primary care (for morphine, methadone and buprenorphine, but not tramadol typically) 5.3: The health technology cannot be appropriately administered until other appropriate health services resources, including staff, are in place? • NO, as no special resources or staff are required. There is already computerised CBT available specifically for alcohol (Reduce Your	Comment noted. No action required. Comments noted. The Committee noted that the provision of psychosocial intervention differs throughout England and as the license for nalmefene mandates the treatment can only be given to patients in combination with psychosocial intervention the relevant health bodies should be provided with sufficient time to organise the service. NICE's Guidance Executive considered the specific circumstances for which it would be appropriate to extend the standard 3 month funding period for relevant health authorities to comply with the recommendations. The Guidance Executive decided that the circumstances were not sufficiently met, and therefore the 3-month funding period was appropriate.

Role*	Section	Comment	Response
		Drinking), and for drugs and alcohol in general (Breaking Free Online). Both require access codes, but the first is free and done by the manufacturer of nalmefene, and the second is paid for but is increasingly being paid for by commissioners. Both are good quality CBT packages, and neither recommends specific drugs. Conclusion In summary we agree with the Committees conclusion that nalmefene plus psychosocial intervention is an important addition to the treatment pathway. However we would suggest that there is a cost-effectiveness comparison with naltrexone for potential use with the same client group. A low complexity psychosocial intervention is all that is needed in this treatment group with high recovery capital and non-dependent drinking. We do not foresee any issues related to discrimination against certain groups or that there would be issues related to offering nalmefene within the normal three month period.	Comment noted. Please see responses above. Comment noted. Please see responses above.
Professional body 1	Conflict	No	
	Declaration	The British Association for Counselling & Psychotherapy (BACP) is recognised by legislators, national and international organisations and the public, as the leading professional body and the voice of counselling and psychotherapy in the United Kingdom, with over 40,000 members working to the highest professional standards in a wide range of settings, including the NHS.	Comment noted. No action required.
	Comments on ACD	The introduction to the consultation document refers to the requirement for health bodies to provide funding to ensure that the health technology is available within three months of the date the recommendation is published by NICE. However the Appraisal Committees first preliminary recommendation is that nalmefene is recommended within its marketing authorisation as an option for reducing alcohol consumption. We would be grateful for clarification of how these two statements interact, i.e. is it intended that nalmefene would be merely an option, rather than a requirement, for clinicians treating patients in the target group, but that local health authorities would be required to make the	Comment noted. Nalmefene is recommended within its marketing authorisation, as an option for reducing alcohol consumption, for people with alcohol dependence who have a high drinking risk

Role*	Section	Comment	Response
		technology available to clinicians?	level (defined as alcohol consumption of more than 60 g/day for men and more than 40 g/day for women, according to the World Health Organization's drinking risk levels) without physical withdrawal symptoms, and who do not require immediate detoxification. See FAD sections 1.1 and 5.1
		The consultation document quotes the technology's marketing authorisation that: Nalmefene should only be prescribed in conjunction with continuous psychosocial support focussed on treatment adherence and reducing alcohol consumption. The consultation document incorrectly states that NICE clinical guideline 115 recommends that psychosocial interventions be delivered by a clinical psychologist. There is in fact no such reference in the guidance, which states (Introduction, p9) rather that: All interventions for people who misuse alcohol should be delivered by appropriately trained and competent staff. Many thousands of counsellors and psychotherapists work in the NHS. They should be considered trained and competent to deliver psychosocial support for alcohol misuse, with brief top-up training where necessary in the specific interventions, if they meet the Department of Health's required standards for psychological therapists, namely: To have completed one-year of recognised full-time (or equivalent part-time) psychological therapy or counselling training leading to a qualification, certification or accreditation recognised by a relevant professional or regulatory body; to have achieved a competency level that fulfils the requirements of the regulatory, accrediting or professional body; to be a member of a relevant professional or regulatory body, and continue to fulfil any accreditation or membership criteria, including meeting requirements for continuing professional and personal development, regular supervision and codes of practice; and to have gained the supervised therapy experience required by the regulatory or professional body encompassing assessment, formulation,	Comments noted. The FAD has been updated to reflect this comment. See FAD section 4.3

Role*	Section	Comment	Response
		engagement, developing the therapeutic relationship, using relevant therapeutic interventions, working collaboratively with clients, and working to end therapy. BACP is the largest professional body for counsellors and psychotherapists in the UK, with over 40,000 members, including many thousands in the NHS, and is among the professional bodies recognised by the Department of Health in relation to the above standards, which all BACP Registered Members and BACP Accredited Members meet. The psychosocial interventions in guideline 115 do not therefore necessarily require delivery by a clinical psychologist, and we are concerned that the propagation of this misunderstanding to clinicians could exacerbate current difficulties in delivering psychosocial support, leading to worse outcomes for patients. We are also concerned at the prospect that recommendations arising from this technology appraisal could be worded to require delivery of psychosocial support by clinical psychologists, rather than by any trained and competent psychological therapist meeting the Department of Health's definition. The consultation document makes several references to NICE clinical guideline 115, the current guidance on alcohol-use disorders available to clinicians. We would be grateful for clarification on how the recommendations arising from the technology appraisal of nalmefene interact with this guidance, specifically whether NICE clinical guideline 115 will be automatically updated as a result, and if not, how clinicians would be advised to treat patients presenting with relevant alcohol-use disorders following publication of the new recommendations.	Comment noted. NICE has produced an 'alcohol-use disorder pathway (2013) which may be up-dated with the recommendations for this appraisal if considered appropriate. See FAD section 6
NHS Professional 3		I am an addiction psychiatrist working in a service covering the whole of Norfolk. My experience with opiate antagonists is primarily with naltrexone as nalmefene is 'red tagged' by our local prescribing committee, but I think they are, in practice virtually interchangeable. Clearly opiate antagonists are not the magic bullet some might hope them to be for alcohol use disorder, however some individuals do very well on them.	Comment noted. No action required

Role*	Section	Comment	Response
		It has always struck me as odd that most of the research done with naltrexone has been on people who are currently (allegedly) abstinent from alcohol as pharmacologically it would only appear to be doing anything when combined with alcohol. The few studies where naltrexone has been given during drinking seem to show some effect in reducing (but not eliminating) this. Additionally the post detox studies show that NTX is primarily effective in averting lapse becoming relapse – which makes sense.	Comment noted. No action required.
		My concern regarding nalmefene is that it is licenced for and targeted, appropriately I think, at the harmful use / mild dependence end of the alcohol use disorder spectrum. This is largely a primary care population. However, in many areas, including ours, local prescribing committees are designating it a secondary care drug. Many people with an alcohol use disorder at this level would not see themselves as requiring specialist care or engage with alcohol services even if advised to do so due to stigma etc. Additionally most clinical alcohol services do not have capacity to take on the whole of this population, focusing more at the severe /dependent end. Specialist services who deal with the harmful use / mild dependence end of the spectrum are generally staffed by counsellors rather than prescribers.	Comment noted. The Committee noted the uncertainty and conflicting opinions among the stakeholders regarding the most appropriate setting for prescribing nalmefene in conjunction with psychosocial support. However the Committee was aware that making specific recommendations about the setting for prescribing nalmefene was outside the scope of a technology appraisal. See FAD section 4.3
		The result is a mismatch between where the drug would be useful and where it is available. Furthermore our service has decided, because of the ban on primary care provision, not to use this drug at all, as those who respond to it may need to take it for an indeterminate period of time and we cannot hand it over to primary care so would end up stuck with a growing burden on our prescribing budget and seeing people long after they need specialist services, which we do not have capacity to do.	Comment noted. The Summary of Product Characteristics states that clinical data for the use of nalmefene under randomised controlled conditions are available for a period of 6 to 12 months. Caution is advised if nalmefene is prescribed for more than 1 year.
		My view is that this is a perfect primary care drug. The dosing is uncomplicated, it is well tolerated and interactions are few and clear. Presently I think GPs are put off, even without the ban, by the requirement for 'psychosocial interventions'. This immediately creates	Comment noted. The Committee noted that the marketing authorisation states that nalmefene should only be prescribed in conjunction with continuous psychosocial support. The Committee

Role*	Section	Comment	Response
		the impression that it is outside of their area of expertise. If it was made clearer that this could mean a FRAMES type brief intervention followed up by a review apt with themselves or the practice nurse a few week later then if no progress had been made starting this medication and reviewing again after a few weeks, it may seem more manageable. The only other thing they have to do is check the person is not heavily dependent to the point of being at risk of complicated withdrawals – which should be well within the skill set of any doctor.	was aware that the NICE clinical guideline 115 recommended, for heavy drinking mild alcohol dependency, that psychosocial intervention (including behavioural therapies, cognitive behavioural therapy and behavioural couples therapies) should consist typically of weekly sessions of 1 hour's duration over a 12-week period and be delivered by appropriately trained and competent staff. The Committee received comments during consultation, suggesting that GPs would require further training to provide psychosocial support to patients. The Committee noted the uncertainty and conflicting opinions among the stakeholders regarding the most appropriate setting for prescribing nalmefene in conjunction with psychosocial support. The Committee also heard from the clinical specialists that although BRENDA is not used in its entirety in clinical practice, most of the components within it are currently provided in the form of brief or extended brief interventions and could be administered by healthcare professionals. However the Committee was aware that making specific recommendations about the setting for prescribing nalmefene was outside the scope of a technology appraisal. See FAD sections 1.2, 4.3 and 4.5
		I regularly speak to GPs about this and they ask where the money is to provide alcohol treatment. My argument is that, given the growing burden of alcohol related morbidity, addressing heavy drinking would save themselves and the NHS time and money, not just in terms of obviously directly linked problems such as liver disease but also (and perhaps mostly) in conditions which are exacerbated or treatment resistant because of the unacknowledged level of drinking such as hypertension, cardiac disease, cognitive decline, gastric problems, skin diseases and mental health problems etc.	Comments noted. No action required.

Role*	Section	Comment	Response
		In summary therefore I feel that this drug has potential to be useful but unless the recommendation is 1. that it should be available and used in primary care 2. that the advice about how to use it seems to fit the skill set and capacity of ordinary GP practices It will not be used at all; and an opportunity to add something to the frankly rather empty looking tool box for GPs wanting to do something about alcohol use in their patients will be lost.	Comment noted. The Committee was aware that making specific recommendations about the setting for prescribing nalmefene was outside the scope of a technology appraisal. See FAD section 4.3

Summary of comments received from members of the public

Theme	Response
Difficult to implement psychosocial intervention in primary care	One healthcare professional commented that it might be difficult to provide the required psychosocial support in primary care. It was also suggested that psychosocial support at the level of BRENDA was not required and psychosocial support could be provided by GPs because only a low level of psychosocial intervention needs to be provided. Another consultee said that GPs are currently not using nalmefene because of the requirement to provide psychosocial support, which they consider outside their area of expertise.
Implementation time scale required	One healthcare professional suggested that an extension to the implementation timeline would be required whereas a healthcare organisation considered the 3 month implementation timescale to be acceptable
Staffing levels	One healthcare organisation suggested that no special staffing resources were required in order to provide psychosocial support and nalmefene treatment. The professional body also commented that the appraisal consultation document incorrectly states that NICE clinical guideline 115 recommends that psychosocial interventions be delivered by a clinical psychologist.
Psychological effect of a tablet	One healthcare professional raised the question of whether prescribing patients with a tablet to treat alcohol dependency may reduce the likelihood of the patient attending the prescribed psychosocial support

Theme	Response
Funding of nalmefene	A healthcare professional stated that it needed to be made clear that local authorities would be expected to pay for this treatment. Comments from a healthcare organisation suggested that funding of pharmacological interventions such as naltrexone was not recognised by Commissioners of the NHS or Directors of Public Health meaning funding for nalmefene may be a problem.
Nalmefene evidence	One healthcare professional suggested that there was a lack of integrity in the nalmefene trials as there appeared to be high dropout rates and the treatment effect was small compared to the placebo group. There was also a question around the mode of action of nalmefene and how it reduces drinking. It was also suggested that the mode of action of nalmefene could cause side effects which are not drink specific.
More detailed comparison with naltrexone	Comments were received suggesting that a more detailed comparison of nalmefene with naltrexone should have been performed as patients who are non-dependant on alcohol are currently treated with naltrexone. It was also suggested that these patients will continue to be treated with naltrexone because it is cheaper than nalmefene.
Nalmefene use in primary or secondary care	One consultee commented that some prescribing committees are designating use of nalmefene to secondary care. This can cause problems for the clinical alcohol services as they do not have the capacity and may also discourage patients from receiving treatment because they do not consider themselves in a position to require specialist care. The consultee commented that there is a mismatch between where nalmefene would be useful and where it is available.