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REVIEW ARTICLE

Nalmefene for Reducing Alcohol Consumption in People with Alcohol Dependence: An Evidence Review Group Perspective of a NICE Single Technology Appraisal

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Abstract As part of its single technology appraisal process, the National Institute for Health and Care Excellence (NICE) invited the company (Lundbeck) marketing nalmefene (Selincro) to submit evidence of its clinical and cost effectiveness for reducing alcohol consumption in people with alcohol dependence. The School of Health and Related Research Technology Appraisal Group at the University of Sheffield was commissioned to act as the independent Evidence Review Group (ERG) and to produce a critical review of the company's submission to NICE. The clinical evidence was derived from three phase III, company-sponsored, randomised, double-blind, placebo-controlled trials in adults with a diagnosis of alcohol dependence comparing nalmefene, taken on an as-needed basis, in conjunction with psychosocial support with placebo in conjunction with psychosocial support. Psychosocial support was provided in the form of BRENDA, an intervention of lower intensity than that recommended in NICE Clinical Guideline 115 (NICE CG115). Post-hoc subgroup analyses were conducted in people who were drinking at high or very high risk levels at baseline and maintained this level of drinking during the screening phase prior to randomisation. This subgroup forms the licensed population. There were a number of limitations and uncertainties in the clinical evidence base which warrant caution in its interpretation. In particular, the post-hoc subgroup analyses and high dropout rates in the three nalmefene studies meant that the inference of treatment effects might be confounded. The company's economic evaluation showed that use of nalmefene in conjunction with psychosocial support in the form of BRENDA dominated the use of BRENDA in conjunction with placebo, providing more quality-adjusted life-years (QALYs) at a reduced cost. However, this evaluation did not meet the final scope issued by NICE, which specified that the comparator should be psychological intervention as defined in NICE CG115. The ERG produced alternative cost per QALY values for the comparison undertaken by the company and suggested three further comparisons deemed relevant: (1) nalmefene with psychological intervention as defined in NICE CG115; (2) delayed use of nalmefene in those who did not respond to psychological intervention as recommended in NICE CG115 alone; and (3) use of naltrexone outside of its marketing authorisation. The ERG thought it probable that using nalmefene in only those people who do not respond to psychological intervention alone was likely to be more cost effective compared with its immediate use in the entire licensed population. The Appraisal Committee accepted the comparison with psychosocial support in the form of BRENDA and believed that the most plausible cost per QALY was likely to be below £5100. Therefore, the Appraisal Committee concluded that nalmefene in conjunction with psychosocial support was a cost effective use of NHS resources compared with psychosocial support alone for treating people with alcohol dependence drinking at a high risk level, without physical withdrawal symptoms and not requiring immediate assisted withdrawal from alcohol.

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Key Points for Decision Makers

Nalmefene, used on an as-needed basis, in conjunction with psychosocial support in the form of BRENDA, resulted in clinically significant reductions in the number of heavy drinking days and total alcohol consumption in people with mild alcohol dependence when compared with placebo in conjunction with BRENDA in the company's trials. However, this level of psychosocial support is much less intensive than the psychological intervention defined in NICE Clinical Guideline 115 (NICE CG115).

The small number of UK people in the nalmefene studies means that the generalisability of these findings to England is unclear. In addition, there are no head-to-head randomised controlled trials comparing nalmefene in conjunction with psychosocial support to naltrexone in conjunction with psychosocial support.

Nalmefene in conjunction with continuous psychosocial support, in the form of BRENDA, appears to represent a cost-effective strategy for people with alcohol dependence who are drinking at a high risk level, without physical withdrawal symptoms and not requiring immediate medically assisted withdrawal from alcohol. However, the cost effectiveness of nalmefene in addition to the psychological intervention defined in NICE CG115 is unknown, as is the cost effectiveness of prescribing nalmefene only to those who did not respond to psychosocial support alone.

The Appraisal Committee recommended nalmefene within its licensed indication. However, specific recommendations about the settings for prescribing nalmefene and the optimal level of psychosocial support were outside the scope of a technology appraisal.

1 Introduction

The National Institute for Health and Care Excellence (NICE) is an independent organisation responsible for providing national guidance on promoting good health and preventing and treating ill health in priority areas with significant impact. Health technologies must be shown to be clinically effective and to represent a cost-effective use of National Health Service (NHS) resources in order for NICE to recommended their use within the NHS in England. The NICE Single Technology Appraisal (STA) process usually covers new single health technologies within a single indication, soon after the UK market authorisation [1]. Within the STA process, the company provides NICE with a written submission, alongside a mathematical model that summarises the company's estimates of the clinical and cost effectiveness of the technology. This submission is reviewed by an external organisation independent of NICE (the Evidence Review Group [ERG]), which consults with clinical specialists and produces a report. After consideration of the company's submission and the ERG report, together with testimony from experts and other stakeholders, the Appraisal Committee formulates preliminary guidance, the Appraisal Consultation Document (ACD), which indicates its initial decision on whether or not to recommend the technology. Stakeholders are then invited to comment on the submitted evidence, and on the ACD, after which a further ACD may be produced or a Final Appraisal Determination (FAD) issued, which is open to appeal. An ACD is not produced when the technology is recommended within its full marketing authorisation; in this case, a FAD is produced directly.

This paper is a summary of the ERG report [2] for the STA of nalmefene for reducing alcohol consumption in people with alcohol dependence and a summary of the subsequent development of the NICE guidance for the use of this drug in England. Full details of all relevant appraisal documents, including the appraisal scope, ERG report, company and consultees submissions, FAD and comments from consultees and commentators can be found on the NICE website [3].

2 The Decision Problem

Harmful drinking is associated with major problems for individuals, their immediate families and friends, and for health and social agencies alike. Persistent harmful drinking is associated with a wide range of social, emotional, behavioural, psychiatric and physical problems which increase the longer the behaviour is maintained. Thus, people drinking harmfully may develop comorbid mental health disorders including depression, anxiety disorders and drug misuse and/or a range of physical comorbidities including neurological, cardiovascular and gastrointestinal disorders, particularly liver injury [4]. Harmful drinking has a negative effect on survival and can reduce life expectancy by 10–12 years.

Harmful drinkers may develop alcohol dependence, which is typically characterised by (1) a compulsion to drink and hence difficulty in controlling alcohol use despite harmful consequences; (2) tolerance to the effects of

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alcohol; and (3) development of a physical withdrawal state if alcohol is suddenly stopped or reduced [5, 6]. Once dependence is established, it tends to run a chronic, relapsing and progressive course [7, 8].

The severity of the alcohol dependence may be defined using measures of symptoms and behaviours together with amounts of alcohol consumed. There are a number of validated instruments for determining both its presence and severity. Thus, the Alcohol Use Disorders Identification Test (AUDIT) is an initial screen for alcohol-related issues while the Severity of Alcohol Dependence Questionnaire (SADQ) measures alcohol-related symptoms, behaviours and consumption which are classified as mild, moderate or severe. The World Health Organization (WHO) categorises alcohol consumption in five health risk levels: abstinent, low, medium, high, and very high risk [9].

Estimates of the overall prevalence of alcohol dependence in England vary from 4 to 6 % [4, 10–12], resulting in an estimated 1.6 million people who are alcohol dependent in England [13]. Of these, only approximately 6 % per year access treatment [11, 12, 14]. The reasons for this include the often long period between developing alcohol dependence and seeking help, the lack of systematic screening and the limited availability of specialist alcohol treatment services in some parts of the country [4].

The NICE clinical guideline on the diagnosis, assessment and management of harmful drinking and alcohol dependence (NICE CG115) [4] recommends a treatment goal of either abstinence or a reduction in alcohol consumption, depending on its severity. For people with mild alcohol dependence, the NICE guideline states that assisted withdrawal programmes are usually not needed and recommends offering psychological intervention in the form of cognitive behavioural therapies, behavioural therapies, behavioural couples therapy or social network and environment-based therapies; these interventions are delivered by appropriately trained and competent staff, typically in weekly 1-h sessions over a 12-week period. Such support is focused specifically on alcohol-related cognitions, behaviour problems and social networks and can be adapted to a goal of total abstinence or to a reduction in consumption. Pharmacological interventions such as acamprosate or naltrexone may also be considered for people with mild alcohol dependence if they do not respond to psychological intervention alone, or if they specifically request it. However, these recommendations, which were based on limited direct evidence for naltrexone in this population and indirect evidence for acamprosate in a population with more severe dependence, do not allow for the fact that neither naltrexone nor acamprosate have current UK marketing authorisation for the reduction of alcohol intake. In addition, access to psychological intervention that is focused on alcohol use is limited in England [15].

For people with moderate alcohol dependence, assisted withdrawal programmes are usually needed but can be managed in a community setting, whereas for people with severe alcohol dependence, medically assisted withdrawal programmes will certainly be needed, usually in an inpatient or residential setting. Pharmacological interventions, such as acamprosate, naltrexone or disulfiram, in combination with psychological intervention may also be considered for people with moderate or severe alcohol dependence who have successfully withdrawn from alcohol to help maintenance of abstinence in the longer term.

Nalmefene, which is an opioid system modulator similar to naltrexone, was granted a European marketing authorisation in February 2013 and was launched in the UK in May 2013. It is indicated 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 [7.5 units/day] for males and more than 40 g/day [5 units/day] for females), according to the WHO drinking risk levels, without physical withdrawal symptoms and who do not require immediate detoxification. It should only be prescribed in conjunction with continuous psychosocial support focused on treatment adherence and reducing alcohol consumption and should be started only in people who continue to have a high drinking risk level 2 weeks after an initial assessment such as an evaluation of the patient's clinical status, social situation, and alcohol consumption pattern (based on patient reporting) [16]. It is administered orally on an 'as-needed' basis with a recommended maximum dose of one 18 mg tablet per day.

NICE issued a final scope to appraise the clinical and cost effectiveness of nalmefene within its licensed indication. If evidence allowed, a wider perspective than the NHS and Personal and Social Services could be presented as sensitivity analyses. The intervention was 'Nalmefene in conjunction with psychosocial support (as defined in NICE Clinical Guideline 115)' with two comparators defined as 'Psychological intervention such as cognitive behavioural therapies, behavioural therapies or social network and environment-based therapies alone (as defined in NICE Clinical Guideline 115)' and 'Naltrexone (in conjunction with psychosocial support as defined in NICE Clinical Guideline 115)'.

3 The Independent Evidence Review Group Review

In accordance with the process for STAs, the ERG and NICE had the opportunity to seek clarification on specific points in the company's submission, in response to which

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the company provided additional information. The ERG also modified the company's decision analytic model to produce an ERG base case and to assess the impact of alternative parameter values and assumptions on the model results. The evidence presented in the company's submission and the ERG's review of that evidence is summarised here.

3.1 Clinical Evidence Provided by the Company

The clinical effectiveness evidence in the company's submission was based primarily on data from three clinical trials—ESENSE1 ($n = 604$) [17–19], ESENSE2 ($n = 718$) [19–21] and SENSE ($n = 675$) [22–24]. All three studies were company-sponsored, European, multi-country, multicentre, randomised, double-blind, parallel-group, phase III clinical trials that compared use of 18 mg oral nalmefene, taken on an as-needed basis, with placebo in people aged 18 years or over, with a Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR) diagnosis of alcohol dependence [5] and at least six heavy drinking days in the preceding 28 days.

People included in the ESENSE 1 and 2 studies had a diagnosis of alcohol dependence with more than six heavy drinking days and average alcohol consumption in the 4 weeks preceding screening in excess of the WHO medium drinking risk level, defined as ≥40 g/day for men and ≥20 g/day for women. People included in the SENSE trial had more than six heavy drinking days in the 28 days prior to enrolment, an average drinking risk level of low risk or greater (84 % were drinking at least at moderate risk level), and <14 consecutive abstinent days in the 4 weeks preceding the screening visit. The total alcohol consumption per day in terms of grams of alcohol was 68 for placebo and 69 for nalmefene in the SENSE trial, 84 for placebo and 85 for nalmefene in ESENSE1 and 88 for placebo and 92 for nalmefene in ESENSE 2. In all three studies, people in the treatment and placebo groups received psychosocial support in the form of BRENDA, focusing on treatment adherence and reduction of alcohol consumption. BRENDA has six components: (1) Biopsychosocial evaluation; (2) Report of the findings of the evaluation; (3) Empathy; (4) addressing the patient's Needs; (5) providing Direct advice; and (6) Assessing the patient's reaction to advice and adjusting the treatment plan as needed. All sessions were provided by trained personnel including the study investigators, nurses and psychologists and were delivered at weekly intervals for the first 2 weeks of the trial and monthly thereafter. The sessions lasted for 15–30 min except for the first session, which lasted for 30–40 min. The ESENSE1 and ESENSE2 trials were identically designed and executed with a follow-up period of 24 weeks. The SENSE trial ran for 52 weeks and was designed primarily to collect safety data although the protocol was later amended to allow an assessment of efficacy.

The co-primary efficacy outcome measures for the ESENSE1, ESENSE2 and SENSE studies were the changes from baseline in the number of heavy drinking days per month, and total alcohol consumption in g/day at month 6. People self-reported their daily alcohol consumption using the timeline follow-back method to estimate retrospectively the number of standard drinks consumed each day; a day was defined as a 24-h period starting at 06:00 h. All efficacy analyses were conducted according to a modified intention-to-treat principle using a mixed model repeated measures approach (MMRM). The company noted that the MMRM analysis used all available data over each month during the treatment period and provided an unbiased estimate of the treatment effect under the assumption that missing data were missing at random.

Between screening and randomisation, a large proportion of prospective trial participants reduced their alcohol intake to below a medium risk level or to less than six heavy drinking days per month, in the month preceding randomisation. These proportions were 18 % in ESENSE1, 33 % in ESENSE2, 39 % in SENSE. As such, they no longer fulfilled the inclusion criteria and any further benefits in terms of a reduction in alcohol intake that might be gained from treatment were limited. To address this issue, the company, following agreement with the Scientific Advisory Group to the European Medicines Agency (EMA), performed post-hoc subgroup analyses to further assess the benefits of treatment with nalmefene and to establish the population that would benefit most from treatment. The company's post-hoc subgroup efficacy analyses included the participants from ESENSE1 ($n = 338$), ESENSE2 ($n = 303$) and SENSE ($n = 183$) who maintained a high or very high drinking risk level between screening and randomisation with alcohol consumption ≥60 g/day [≥7.5 units/day] for men and ≥40 g/day [≥5 units/day] for women. The subsequent marketing authorisation was granted for this subgroup of people only who thereby form the licensed population [25].

The main finding of the post-hoc analyses in the licensed population was that the reductions in heavy drinking days and total alcohol consumption were significantly greater in people treated with nalmefene in conjunction with BRENDA than in those receiving placebo in conjunction with BRENDA (Table 1).

The company also presented a post-hoc pooled analysis (not meta-analysis) of the individual patient level data of the ESENSE1, ESENSE2 and SENSE studies. This showed that after 6 months nalmefene in conjunction with BRENDA significantly reduced the number of heavy drinking days by −3.01 days/month (95 % CI −4.36 to

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Table 1 Main efficacy endpoints in the ESENSE1, ESENSE2 and SENSE trials for patients with a high/very high drinking risk level at baseline and randomisation (i.e., the licensed population)

Outcomes	Trials	Number of participants at baseline		Mean difference to placebo in the change from baseline to month 6	95 % CI	*p* value
		Nalmefene in conjunction with psychosocial support[a]	Placebo in conjunction with psychosocial support[a]			
Heavy drinking days	ESENSE1	171	167	−3.7 days/month	−5.9 to −1.5	0.001
	ESENSE2	148	155	−2.7 days/month	−5.0 to −0.3	0.025
	SENSE	141	42	−2.6 days/month	−5.5 to 0.2	0.071
				−3.6 days/month[b]	−6.5 to −0.7[b]	0.016[b]
Total alcohol consumption	ESENSE1	171	167	−18.3 g/day	−26.9 to −9.7	<0.0001
	ESENSE2	148	155	−10.3 g/day	−20.2 to −0.5	0.040
	SENSE	141	42	−15.3 g/day	−29.1 to −1.5	0.031
				−17.3 g/day[b]	−30.9 to −3.8[b]	0.013[b]

CI confidence interval

[a] Psychosocial support provided as a motivational and adherence enhancing intervention (BRENDA) to support change in behaviour and improve adherence to treatment. This was delivered at weekly intervals for the first 2 weeks and monthly thereafter (sessions limited to approximately 15–30 min except for the first session [administered at randomisation] which was approximately 30–40 min)

[b] At the start of month 13. SENSE had a longer follow-up period than ESENSE1 or ESENSE2

−1.66, $p < 0.0001$) and total alcohol consumption by −14.22 g/day (95 % CI −19.96 to −8.47, $p < 0.0001$) compared with placebo in conjunction with BRENDA. Following a request from the ERG and NICE, the company undertook a meta-analysis, but these results were marked as academic in confidence and so cannot be presented.

Safety data were recorded for all three nalmefene trials (ESENSE1, ESENSE2 and SENSE) for both the total and licensed populations. In the pooled subgroup of people with at least a high drinking risk level at screening and randomisation, the percentage of treatment-emergent adverse events were slightly higher than those in the total population. Nausea, dizziness, insomnia and headache were the most commonly reported adverse events and they occurred more frequently in the pooled nalmefene in conjunction with BRENDA group as compared with the pooled placebo in conjunction with BRENDA group. The duration of the frequent adverse events in the nalmefene group was typically a few days in both the total and licensed population with a median duration of ≤8 days. In the licensed population, higher rates of patient withdrawal were observed during the treatment period in the pooled nalmefene in conjunction with BRENDA group (224/475 [47.2 %]) compared with the pooled placebo in conjunction with BRENDA group (133/369 [36.0 %]). The main reasons for study discontinuation were withdrawal of consent and adverse events. Similar results were observed for the pooled total population (491/1144 [42.9 %] versus 270/797 [33.9 %], respectively).

In the absence of any direct head-to-head randomised controlled trials (RCTs) comparing nalmefene in conjunction with psychosocial support with naltrexone in conjunction with psychosocial support, the company determined whether a network meta-analysis could be conducted to compare the effect of naltrexone in conjunction with psychosocial support with nalmefene in conjunction with psychosocial support for the reduction of alcohol consumption in actively drinking adults with mild alcohol dependence. The company's systematic review identified three RCTs (representing four published citations) [26–29]; however, all three studies had limitations. For example, data were not reported on several key variables such as total alcohol consumption; drinking levels at baseline; drinking outcomes; and the numbers of evaluable participants, thus making them ineligible for inclusion in a network meta-analysis.

3.1.1 Critique of the Clinical Evidence and Interpretation

1. Completeness of the data search
   The ERG believes that the company undertook a comprehensive systematic review of the current literature and that all relevant studies for nalmefene in conjunction with psychosocial support were included. However, it was unclear whether all the extractable naltrexone data had been included as the company did not provide information on whether or not they had

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contacted the authors of the naltrexone studies to request additional unpublished data.

2. The strength of the post-hoc analysis

The clinical effectiveness data for nalmefene were taken from three RCTs of good methodological quality but the post-hoc combined subgroup analyses of people who had a high or very high drinking risk level may have resulted in less robust efficacy and safety data because the effect of initial randomisations may have been lost. In addition to the known limitations of post-hoc subgroup analyses [30], Sun et al. [31] suggest that the credibility of subgroup effects, even when claims are strong, is usually low. However, a Scientific Advisory Group, which was consulted by the EMA during the regulatory process for nalmefene, recognised the validity of the post-hoc analysis for defining the target population and acknowledged that whilst post-hoc analyses are not ideal, they are commonly used in clinical trials for psychiatric drugs [25].

3. The effect of the high drop-out rate on the robustness of the findings

The high dropout rates in the three nalmefene studies may further limit the robustness of the findings. The company undertook several sensitivity analyses to account for missing data but there were inconsistencies in the reported differences between treated and placebo groups. As a result, the EMA noted a degree of uncertainty about the exact magnitude of benefit [25]. In the nalmefene trials all participants self-reported their alcohol intake, thus this subjective measure could have biased the results. However, the company noted that the timeline follow-back method, used in the ESENSE 1, ESENSE 2 and SENSE trials, provides reliable, albeit self-reported data on drinking behaviour [32–35].

4. Uncertainty about the effectiveness of the psychosocial support compared with psychological intervention as defined in NICE CG115

The ERG noted that a key uncertainty in the clinical evidence related to the type, frequency and duration of the psychosocial support provided in the RCTs and how generalisable this might be to practice in England. In the ESENSE1, ESENSE2 and SENSE trials, psychosocial support was provided in the form of BRENDA. This was used in accordance with the EMA guideline on the development of medicinal products for the treatment of alcohol dependence [36], which states that standardised psychosocial interventions should be allowed in alcohol dependence studies and kept to a constant and low level for all people. In the nalmefene trials, BRENDA was delivered by the study investigators, nurses or psychologists at weekly intervals for the first 2 weeks and monthly thereafter; sessions were limited to approximately 15–30 min except for the first session which was administered at randomisation and lasted approximately 30–40 min. This is in contrast to the recommendation in NICE CG115 [4] that psychological intervention in the form of, for example, cognitive behavioural therapy or behavioural couples therapy should be delivered, typically by a clinical psychologist, in weekly 1-h sessions over a 12-week period [4]. It is not clear how the efficacy of nalmefene would have been affected if trial participants had received psychological intervention as defined in NICE CG115.

5. Duration of treatment

The duration of treatment in the nalmefene trials ranged from 6 months (ESENSE1 and ESENSE2) to 1 year (SENSE trial). Adherence rates (defined as a day when there was alcohol consumption and concomitant nalmefene medication intake or a day when there was no alcohol consumption) ranged from 75.7 % in ESENSE1 to 86.7 % in the SENSE trial in the licensed population. No information is available on the efficacy and safety of nalmefene after 12 months' treatment duration. The Summary of Product Characteristics for nalmefene advises caution if the drug is prescribed for more than 1 year [16]. Nevertheless, in the company's base case it was assumed that those who had reduced alcohol consumption to a medium risk level at 12 months would remain on nalmefene whilst at this risk level.

6. Applicability of the trial results

The populations in the ESENSE1, ESENSE2 and SENSE trials were predominantly White (>99 %) with a mean age of 48 years in the ESENSE trials and 44 years in the SENSE trial. Only a small minority of trial participants were from the UK; no UK centres participated in the ESENSE trials and in the SENSE trial UK sites comprised only 5/156 (3.2 %) of the total; no data were provided on inter-country variability in outcomes. The ESENSE1 and ESENSE2 trials excluded people with co-morbid psychiatric conditions and SENSE excluded people with severe psychiatric conditions. However, the company commented in its submission that many alcohol-dependent people have diagnosed medical conditions and/or psychiatric comorbidities. In addition, people were excluded if their serum transaminase levels were over three times the upper laboratory reference range or if they were taking certain concomitant medication such as drugs for angina, anticoagulants, anticonvulsants, insulin, sedatives and systemic steroids. Thus, it is unclear how well the study results can be extrapolated to older people, non-Caucasian populations and those

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with the mental health and physical co-morbidities excluded from the studies. Furthermore, there must be some uncertainty regarding the generalisability of these data to people in England.

3.2 Cost-Effectiveness Evidence

The company conducted a systematic review on the cost effectiveness of nalmefene in the treatment of alcohol dependence. As no suitable studies were found, they developed a de novo economic model, constructed in Microsoft Excel®, to estimate the cost effectiveness of as-needed nalmefene in conjunction with psychosocial support compared with psychosocial support alone.

The model was constructed using a cohort Markov approach which consisted of a short-term phase (1 year based on the nalmefene clinical trials) with 1-month cycles and a long-term phase (up to 5 years using extrapolated trial results) with 1-year cycles. The 1-month cycle length in the short-term phase was used to align with the follow-up in the trials, that is, heavy drinking days and total alcohol consumption over 28 days. The short-term phase aimed to take account of treatment efficacy and patient adherence and observed treatment discontinuation, incidence of alcohol-attributed harmful events and deaths. The long-term phase aimed to model the maintenance of effect of treatment, patient progression and the incidence of alcohol-attributable harmful events and deaths. A 1-year cycle length was used by the company in the long-term phase because 1-year evidence for the maintenance and recurrence of heavy drinking after an initial response to treatment and second-line treatments was available. Additionally, the 1-year cycle also reduced the number of assumptions and uncertainties the company considered were necessary. Half-cycle correction was not incorporated because the company considered these to be negligible because the initial cycles were a month long. The model structure was designed to reflect the treatment pathway in England, used a NHS and PSS perspective, and discounted both future costs and benefits at 3.5 % per annum.

The characteristics of the population used in the model were based on pooled data from the trial participants who met the licensing criteria in the ESENSE1, ESENSE2 and SENSE trials. Thus, the hypothetical populations comprised adults with a mean age of 48 years at the start of the model, of whom 69 % were male. Overall, 42.5 % were in the high risk drinking level and 57.5 % in the very high risk drinking level on entry to the model with alcohol dependence defined according to the WHO definition of drinking risk.

Transition probabilities in the first year between WHO-defined drinking states were derived using pooled data from the ESENSE1, ESENSE2 and SENSE trials. In addition to drinking level states the model contained health states for people who experience serious alcohol-attributable harmful events; temporary alcohol-attributable harmful events; and for those who die. The company stated that the alcohol-attributable harmful events included in the model were 'chosen because they incur a significant cost for the healthcare system and because the association between alcohol consumption and these events has the strongest published evidence. These events also occur in the assessed population of patients and within the chosen 5-year time horizon. These specific events were also identified and implemented in the model based on the advice received by the company from clinical and epidemiological experts, including assessment of the available evidence in the literature'. Within the model the risks of experiencing serious and temporary events increased with the drinking risk severity.

Serious events were ischaemic heart disease, haemorrhagic stroke, ischaemic stroke, cirrhosis of the liver and pancreatitis. People who experienced a serious event discontinued treatment immediately and remained in that serious event health state for the remainder of the model or until death. Hence, people could only experience a single serious event. People with serious events were not allocated to any drinking risk level on the assumption that the costs incurred and utility loss due to the serious event would be of a greater magnitude than those associated with drinking risk level.

Temporary events were lower respiratory tract infections, transport-related injuries and injuries not related to transport. Contrary to the assumptions made following a serious event, the drinking risk level of the patient was maintained alongside the temporary health state. People who experienced temporary events incurred an additional cost and a utility decrement but did not discontinue treatment. People could experience more than one temporary event within the model time horizon although not simultaneously.

People could die at any point in the model. The mortality rate was assumed to comprise three distinct elements: mortality associated with experiencing a serious event; mortality associated with experiencing a temporary event; and background mortality associated with other causes, the rates of which were set to those for an age- and gender-matched general population.

The model allowed people to discontinue treatment in accordance with observed rates within the RCTs. People who discontinued treatment due to nalmefene-related adverse events such as nausea, dizziness, insomnia or headaches were assumed to switch to psychosocial support alone. People who discontinued treatment for non-nalmefene-related reasons were assumed to receive no further

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treatment and to immediately transition to either the high risk drinking level state (42.5 %) or the very high risk drinking level state (57.5 %) as at model entry. People who received no treatment were assumed to maintain their allocated drinking risk level for the remainder of the initial year. The assumed risks of serious and temporary events in the model are provided in the ERG report [2].

At the end of the 1-year short-term phase, people were divided into three drinking risk groups: abstinent or low risk, medium risk, or high or very high risk. Those people who were in the high- or very high-risk category at the end of the first year were assumed to need medically assisted withdrawal from alcohol followed by treatment with naltrexone or acamprosate together with psychosocial support. This assumption was based on advice from "clinical experts practising in and/or based in the NHS in England". It was assumed that people who dropped out from nalmefene and psychosocial support or from psychosocial support alone would undergo medically assisted withdrawal from alcohol.

Those people who were in the abstinent or low-risk drinking group at the end of the short-term phase were assumed to need no further treatment. However, these people were at risk of relapse. People who experienced a relapse were allocated to either the high risk drinking level state (42.5 %) or the very high risk drinking level state (57.5 %) and assumed to return to the same treatment they had initially received. Within years 2–5 the costs incurred and QALYs accrued in each cycle for people who relapsed were assumed to equal the average costs, and the average QALYs for people on nalmefene and psychosocial support, or psychosocial support alone, within the initial short-term phase.

Those people who were drinking at a medium risk level at the end of the short-term phase were assumed to continue with the same treatment. It is reported in the company submission that "According to clinical experts in England and Wales consulted by Lundbeck this is aligned with clinical practice considering the risk of acute and chronic harms for this level of drinking". If the patient transitioned to the abstinent/low risk drinking levels then treatment would be discontinued; if the patient transitioned to high or very high risk drinking levels it was assumed that they would receive secondary treatment with naltrexone or acamprosate and psychosocial support.

Transition probabilities in subsequent years were based on information from several sources. Transition probabilities in the abstinent or low risk drinking levels were based on data from Taylor et al. [37] which estimated a relapse to heavy drinking of 19 % per annum; those in the medium risk drinking level were calculated from the SENSE RCT with the company stating that these "were derived from the average transition probabilities of the medium-risk drinking level for the last 6 months of the SENSE 12-month trial"; while those in the high risk/very high risk drinking levels were based on data provided in a network meta-analysis undertaken in NICE CG115 [4], which estimated that the probability of relapse to heavy drinking at 12 months was 0.8176 (95 % Credible Interval 0.3894–0.9996) for acamprosate and psychosocial support and 0.8253 (95 % Credible Interval 0.4095–0.9997) for naltrexone and psychosocial support. The company used the data for acamprosate and psychosocial support in their modelling and, on the basis of clinical opinion, used the assumption that people who relapse following treatment with either naltrexone or acamprosate and psychosocial support have a 50 % probability, each year, of receiving further treatment with naltrexone or acamprosate with psychosocial support and a 50 % probability of remaining in the high risk/very high risk drinking levels.

In addition to health states, the model could incorporate the effect of alcohol consumption on crime and justice, hence providing a wider societal perspective. The inclusion of a societal perspective was within scenario analyses and was not included within the company's base case. The company submission cited Anderson and Baumberg [38], who reported that in England and Wales 25 % of all crimes; 48 % of violent crime; 19 % of robbery; and 58 % of sex offenses/rape were undertaken by people under the influence of alcohol, or were alcohol-related. To estimate the costs associated with crime the company applied methods reported by the University of Sheffield [39] for a NICE Public Health guideline (PH 24) [40].

The costs of nalmefene, taken on an 'as-needed' basis, were estimated at £620 per patient per year. It was assumed that people would be seen by their GP on 75 % of occasions at a cost of £63 per appointment and at a specialist care drug and alcohol service on the remaining 25 % of occasions at a cost of £94 per appointment. Thus, the cost for the psychological support component would equate to £991 per annum. A weighted average cost for medically assisted withdrawal from alcohol was assumed to be £1404.

The utility in the first year was taken from pooled data from the ESENSE1, ESENSE2 and SENSE RCTs. In the ESENSE trials, the EuroQol 5-dimension (EQ-5D) questionnaire was administered at baseline and at weeks 12 and 24 while in the SENSE trial the same questionnaire was administered at baseline, weeks 12, 25, 36 and 52. The area under the curve was estimated every 3 months from baseline to 1 year adjusted for the baseline utility, and assuming a linear transition between the mean utilities at each time point. The assumed mean utility values for nalmefene in addition to psychosocial support were: 0.79 (baseline); 0.82 (12 weeks); 0.83 (24 weeks); 0.84 (36 weeks); and 0.87 (52 weeks). Corresponding values for placebo in addition to psychosocial support were 0.79

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(baseline); 0.80 (12 weeks); 0.81 (24 weeks); 0.83 (36 weeks); and 0.84 (52 weeks).

In years 2–5, utility was assumed to be a function of drinking status. Without serious or temporary events the assumed mean utility values were 0.79 for those with a high or very high drinking status, 0.82 for those in a medium drinking state, and 0.86 for those who were abstinent or in a low drinking state. Data from the naturalistic STREAM study which was undertaken in primary care in the UK were used in a sensitivity analysis [41]. These data showed a much larger utility difference (0.285) between those drinking at a very high risk level and those who were abstinent.

The company provided the incremental cost effectiveness ratio (ICER) in terms of cost per QALY gained for a base-case analysis and the results from sensitivity analyses (Table 2). In addition, a threshold analysis was presented that indicated that the efficacy difference between nalmefene together with psychosocial support and placebo together with psychosocial support would need to be reduced by 70.3 % for nalmefene and psychosocial support to have a cost per QALY of £20,000. Further analyses that varied the assumptions in relation to those drinking at a medium risk level made no difference to the results.

3.2.1 Critique of the Cost-Effectiveness Evidence and Interpretation

The de novo model developed was appropriate for the decision problem and was generally well described within the company's report. The model structure was considered by the ERG to be based on generally reasonable data sources; to be well constructed with only minor errors; and clinically appropriate.

The ERG noted that in the company's base case, the net impact of the favourable and unfavourable assumptions made when estimating the cost effectiveness of nalmefene and BRENDA were likely to be unfavourable to nalmefene. The assumptions likely to be unfavourable to nalmefene include a time horizon of 5 years; the lack of an increase in mortality rates for those with serious and temporary events; only one serious event was permitted; drinking risk levels were considered irrelevant after the occurrence of a serious event; and use of the lower bounds and uninflated costs for a medically assisted withdrawal from alcohol. The assumptions favourable to nalmefene included over-estimation of the rates of serious and temporary events; over-estimation of crime rates, although not included in the base case; the high proportion of people, according to the ERG clinical advisors, undergoing inpatient medically assisted withdrawal from alcohol; the requirement for all people who continue to drink at high or very high risk levels at 12 months to undergo medically assisted withdrawal; drug wastage was not included in the base case as it was thought by the company not to be an issue; the lack of imputation for dropouts in the utility calculation in the first year and the fact that nalmefene-related adverse events were not incorporated in terms of costs throughout the modelling horizon and disutility beyond the first year.

There were some areas of disagreement and contention:

1. Appropriateness of the psychosocial support assumed
   Within the model the psychosocial component was represented by BRENDA as employed in the three nalmefene trials. The ERG noted that use of BRENDA contrasts strongly with the recommendations for psychological intervention as defined in NICE CG115. Thus, the evaluation undertaken in the model does not meet that specified in the final NICE scope, which stipulates that the comparator should be psychological intervention as defined in NICE CG115. The company assumed that psychosocial support in the form of BRENDA would be provided by GPs on 75 % of occasions and within a specialist drugs and alcohol service for the rest of the time. However, clinical advisors to the ERG felt that the proportion of visits undertaken in specialist care would be much higher were best practice followed.
2. Duration of treatment
   The ERG clinical advisors did not agree with the company's assumption that people would remain on treatment for the full year, regardless of drinking level. They felt that GPs would not allow people to continue to drink at high and more particularly at very high risk levels for more than 6 months, and more likely 3 months, before recommending intensification of treatment and additional specialist input. The ERG raised this issue with the company during the clarification process; the company maintained their position but did not provide any evidence to support the contention that all people would meet the criteria for medically assisted withdrawal at 12 months rather than at 6 or 60 months.
3. Missing comparisons
   The main limitation of the company's cost-effectiveness analysis was that no formal comparison was performed between nalmefene in conjunction with psychosocial support and psychological intervention alone, where the psychological intervention was provided as defined in NICE CG115 [4]. A further key limitation was that no comparison with naltrexone used outside of its marketing authorisation in

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Table 2 Scenario analyses results from the economic model presented by the company

Scenario analysis	Total costs (£)		Total LYs		Total QALYs		Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER
	NMF + PS	PS	NMF + PS	PS	NMF + PS	PS				
Base-case analysis	4445	4842	4.413	4.404	3.624	3.553	−397	0.009	0.071	NMF + PS dominates
Time horizon reduced to 1 year	1571	1162	0.959	0.957	0.800	0.784	408	0.002	0.017	£24,684
Societal perspective included	15,632	18,524	4.413	4.404	3.624	3.553	−2893	0.009	0.071	NMF + PS dominates
Time horizon reduced to 1 year and societal perspective included	4999	5094	0.959	0.957	0.800	0.784	−95	0.002	0.017	NMF + PS dominates
NMF intake assumed to be every day rather than as-needed	4863	4842	4.413	4.404	3.624	3.553	21	0.009	0.071	£289
No second-line treatment options allowed	2959	2521	4.406	4.394	3.569	3.483	438	0.012	0.086	£5090
Using utility values from the STREAM study	4445	4842	4.413	4.404	3.122	2.929	−397	0.009	0.192	NMF + PS dominates
An assumption that PS was associated with zero costs	4254	3678	3.624	3.553	3.624	3.553	576	0.071	0.071	£8088

Dominates means the intervention provides more QALYs at a lower cost

ICER incremental cost effectiveness ratio (in terms of cost per QALY gained), *LY* life-year, *NMF* nalmefene, *PS* psychosocial support, *QALY* quality-adjusted life-year

conjunction with psychosocial support was made as requested in the scope.

3.3 Additional Work Undertaken by the Evidence Review Group

The ERG noted that the decision problem could not be fully evaluated using the data currently available. They considered that four relevant comparisons could be formulated and the ability to provide robust estimates of the cost effectiveness of nalmefene in addition to psychosocial support decreased as the comparisons became more relevant to the decision problem. The four comparisons were:

1. Nalmefene in conjunction with psychosocial support compared with psychosocial support alone when the support was provided using BRENDA as in the pivotal RCTs.
2. Nalmefene in conjunction with psychosocial support compared with psychological intervention alone when the psychological intervention was provided in line with NICE CG115 recommendations.
3. Delayed use of nalmefene in people who did not respond to psychological intervention provided in line with NICE CG115 recommendations compared with the immediate use of nalmefene in addition to psychological intervention provided in line with NICE CG115 recommendations.
4. Delayed or immediate use of nalmefene in people who did not respond to psychological intervention as recommended in NICE CG115 with off-label use of naltrexone in addition to psychological intervention provided in line with NICE CG115 recommendations in those who did not respond to this type of psychological intervention alone.

3.3.1 Results of the Additional Comparisons

None of the analyses undertaken by the ERG markedly changed the ICER calculated by the company. The one notable difference was the likely cost effectiveness of only using nalmefene in those people who do not respond to

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psychological intervention alone within a clinician-defined time frame rather than using it in all eligible people in the licensed population. Although an ICER for this comparison could not be estimated precisely by the ERG, it believed that delayed treatment reserved for those who do not respond to psychosocial support alone was more cost effective than immediate treatment for all people as not all people would require nalmefene treatment. Whilst comparison 4 was considered by the ERG, an ICER could not be estimated.

3.3.1.1 Comparison 1 In this comparison the cost per QALY gained does not rise above £6000 (Table 3).

3.3.1.2 Comparison 2 The results of the threshold analysis, assuming people drinking at a medium risk level remained on treatment and ignoring societal costs, were similar to those produced by the company, namely, if the efficacy of nalmefene and psychosocial support compared with psychosocial support in conjunction with placebo were reduced by 62.8 %, then the cost per QALY would become £20,000. The reduction would have to be of 71.5 % for the cost per QALY to reach £30,000 (Fig. 1). The ERG clinical advisors did not wish to venture an opinion on whether the actual reduction would be greater or lower than a 60–70 % threshold.

3.3.1.3 Comparison 3 Very few data are available to enable the cost effectiveness of nalmefene in comparison 3 to be assessed. The company's model estimated that, when psychosocial support was provided with BRENDA, over 20 % of people were either abstinent or drinking at low risk levels at month 3. The ERG clinical advisors felt that the response rate was likely to be higher with the more intense psychological intervention recommended in NICE CG115. The ERG thought it probable that in people supported in this way, the costs of nalmefene can be saved without incurring health losses, which could be a more cost-effective strategy.

3.3.1.4 Comparison 4 Very few data are available to enable the cost effectiveness of nalmefene in comparison 4

Table 3 Exploratory analyses undertaken by the Evidence Review Group (ERG) in comparison 1

Code	Change from CS base case	Total costs (£)		Total QALYs		Incremental costs (£)	Incremental QALYs	ICER
		NMF + PS	PS alone	NMF + PS	PS alone			
CS base case		4445	4842	3.624	3.553	−397	0.071	NMF + PS dominates
1	Medium-risk drinkers assumed to relapse to high/very high risk	4803	5240	3.608	3.538	−437	0.070	NMF + PS dominates
2	Utility for NMF + PS and for PS alone set to 0.82 in the first year	4445	4842	3.613	3.558	−397	0.055	NMF + PS dominates
3	All people who withdraw for NMF-related reasons also withdraw from PS	4685	4842	3.607	3.553	−157	0.055	NMF + PS dominates
4	Half of people who withdraw for NMF-related reasons also withdraw from PS	4565	4842	3.616	3.553	−277	0.063	NMF + PS dominates
5	Assuming an average cost of medically assisted withdrawal of £645 per patient	4186	4438	3.624	3.553	−253	0.071	NMF + PS dominates
6	Costs of specialist prescribing face-to-face contact set to £119	4560	4945	3.624	3.553	−385	0.071	NMF + PS dominates
7	Costs of serious or temporary events set to £0 and associated utility set to that of very high risk drinkers	3625	3811	3.685	3.623	−186	0.062	NMF + PS dominates
ERG base case	1 + 4 + 5 + 6	4624	4849	3.601	3.538	−226	0.063	NMF + PS dominates
ERG base case but no second-line treatment options are allowed		2954	2578	3.528	3.455	377	0.073	£5166

Dominates means the intervention provides more QALYs at a lower cost

CS company submission, *ICER* incremental cost effectiveness ratio (in terms of cost per QALY gained), *NMF* nalmefene, *PS* psychosocial support, *QALY* quality-adjusted life-year

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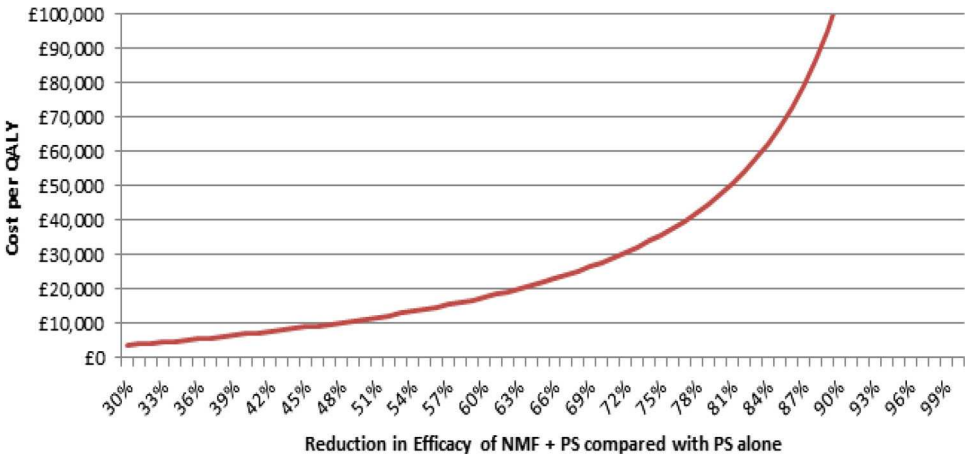

Fig. 1 Threshold analysis of the efficacy of nalmefene and psychosocial support, provided in line with NICE CG115 guidance, compared with psychosocial support in conjunction with placebo. *NMF* nalmefene, *PS* psychosocial support, *QALY* quality-adjusted life-year

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to be assessed. As such, the ERG did not feel comfortable in providing either an estimate of the ICER for this comparison or a view on the likely cost effectiveness of nalmefene in this comparison.

3.4 Conclusions of the Evidence Review Group Report

The clinical evidence provided in the company's submission, which was based on the results of three pivotal trials, confirmed the efficacy and safety of treatment with nalmefene together with psychosocial support. However, there were a number of limitations and uncertainties in the evidence base which warrant caution in the interpretation of the data. In particular, the inference of treatment effects may be confounded by the high drop-out rates and the use of post-hoc subgroup analyses to define the licensed population.

The base case results in the company's economic evaluation in which the psychosocial support in both the intervention and comparator groups was BRENDA, an intervention of lower intensity than that recommended in NICE CG115, use of nalmefene with psychosocial support dominated psychosocial support alone. The ERG's base case also estimated that the use of nalmefene was dominant in this comparison and had a similar threshold reduction in the relative effectiveness of nalmefene and psychosocial support compared with psychosocial support at which the cost per QALY gained was £20,000. However, this evaluation did not meet the final scope issued by NICE, which specified that the comparator should be psychological intervention as defined in NICE CG115. The ERG considered three further comparisons although there were insufficient data to allow a robust evaluation. Nevertheless, the ERG believed it likely that initially providing psychosocial support alone and reserving the use of adjunct nalmefene for those who did not benefit would be more cost effective than the immediate use of nalmefene with psychosocial support for all.

4 Key Methodological Issues

The methodological issue that had the largest impact on the results and interpretation of the economic evaluation was related to the fact that the pivotal RCTs did not use the psychosocial support listed in the scope. This means that all cost-effectiveness analyses must be subject to considerable uncertainty. A secondary methodological issue was that a formal evaluation against the most relevant pharmaceutical comparator, naltrexone, was not undertaken, although the ERG note that data to allow this were not identified by the company.

5 National Institute for Health and Care Excellence Guidance

In October 2014, on the basis of the evidence available, including verbal testimony from invited clinical experts and patient representative, the Appraisal Committee produced final recommendations that nalmefene was recommended, within its market authorisation, for reducing alcohol consumption in people with alcohol dependence who have a high drinking risk level, defined as alcohol consumption of more than 60 g per day for men and more than 40 g per day for women, according to the World Health Organization's drinking risk levels, without physical withdrawal symptoms who do not require immediate medically assisted withdrawal from alcohol. It should only be prescribed in conjunction with continuous psychosocial support focused on treatment adherence and reducing alcohol consumption and should only be initiated in people

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who continue to drink at a high risk level 2 weeks after an initial assessment.

5.1 Consideration of Clinical and Cost-Effectiveness Issues Included in the Final Appraisal Determination

The full list of the issues considered by the Appraisal Committee can be found in the FAD [42].

The key issues are described in the following sections.

5.1.1 Current Clinical Management

The Appraisal Committee considered the current clinical management of alcohol consumption in people with alcohol dependence who have a high drinking risk level, without physical withdrawal problems and who do not require immediate medically assisted withdrawal from alcohol. Clinical specialists advised the Appraisal Committee that psychosocial support in the form of a brief or an extended brief intervention was standard first-line treatment for these people and that the provision of psychosocial support differed throughout England. However, the intensity, duration and frequency of these interventions were almost invariably less than those recommended in NICE CG115 [4]. The Appraisal Committee also noted that BRENDA, the psychosocial support provided in the nalmefene studies, is not used in routine UK clinical practice, although several of its components overlap with those used in the brief or extended brief interventions currently employed. The Committee accepted that BRENDA closely resembled current established practice and concluded that psychosocial support in the form of a brief or extended brief intervention was a valid comparator for this appraisal.

5.1.2 Uncertainties in the Clinical Evidence

The Appraisal Committee noted that the licensed population in the marketing authorisation for nalmefene had been identified following post-hoc subgroup analyses of trial data. Although the subgroup analysis had not been prespecified, it was performed because 18 % (ESENSE1), 33 % (ESENSE2) and 39 % (SENSE) of potential trial participants reduced their drinking between screening and randomisation, thereby leaving little scope for additional improvement. The ERG had concerns about the robustness of the subgroup efficacy data as none of the nalmefene studies were powered for this analysis and the balance between treatments of known and unknown covariates may have been lost. Despite this, the Appraisal Committee decided that the post-hoc subgroup analyses were sufficiently robust to be used in its decision making and were aware that the European Medicines Agency recognised the validity of the subgroup analyses and that these analyses formed the basis of the licensed population in the marketing authorisation for nalmefene. However, the Appraisal 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 to the provision of psychosocial support. The clinical experts present at the committee meeting commented that although these outcomes appear modest, they are clinically significant. The Appraisal Committee concluded that nalmefene in conjunction with BRENDA reduced the number of heavy drinking days and total alcohol consumption compared with BRENDA in conjunction with placebo, although the exact magnitude of the effect was uncertain because of the post-hoc subgroup analyses.

5.1.3 Relevance of Trial Data to UK Clinical Practice

The Appraisal Committee considered the relevance of the nalmefene trials to clinical practice in the UK. The ESENSE trials were conducted outside the UK and only five (3.2 %) UK sites were included in the 156-site SENSE trial. People with severe psychiatric conditions or severe medical comorbidities were excluded from the ESENSE trials and in the majority of centres recruiting for the SENSE trial. Although individuals with stable psychiatric comorbidities and those taking multiple medications were included at the UK sites, no site-specific data were provided. The ERG and clinical specialists noted that alcohol dependent people often have significant alcohol-related psychiatric and physical comorbidities but the Appraisal Committee concluded that while the baseline characteristics of the populations in the three nalmefene studies were not wholly generalisable to clinical practice in England, they were sufficiently similar to aid clinicians to identify the appropriate patient population for treatment with nalmefene in conjunction with psychosocial support.

5.1.4 Uncertainties in the Economic Modelling

The Appraisal Committee discussed whether the company's assumption that people would remain on treatment for 12 months regardless of drinking level and response was reasonable. The clinical specialist agreed with the ERG that it is unlikely that GPs would allow a patient to continue at a high drinking risk level for up to 1 year. The Appraisal Committee considered whether the utility values used in the economic model incorporated all the health-related quality-of-life benefits associated with a reduction in alcohol consumption. The Appraisal Committee was

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aware that it had heard from patient experts that reducing alcohol consumption was of considerable importance to family members and carers. The Appraisal Committee agreed that the utility values used in the economic model may have underestimated the true benefit of nalmefene in conjunction with psychosocial support. Although aware of the uncertainty whether the results from the three clinical nalmefene studies are generalisable to people seen in practice in England and the uncertainty associated with the post-hoc subgroup analyses, the Committee agreed that by taking into account the wider societal perspective and the possible underestimation of the utility values, the most plausible ICER was likely to be lower than £5100 per QALY gained.

6 Conclusion

The evidence suggests that in people with alcohol dependence who are drinking at high risk levels, but who do not have physical withdrawal symptoms and do not need immediate medically assisted withdrawal from alcohol, nalmefene in conjunction with psychosocial support is a clinically and cost effective option for reducing alcohol consumption when compared with the provision of psychosocial support alone. However, an important point highlighted by this STA is that the Appraisal Committee accepted BRENDA as an appropriate addition to nalmefene and as a comparator despite this being different from the psychosocial intervention explicitly listed in the scope, which was that defined in NICE CG115. In the FAD it is stated that "the psychosocial intervention in the guideline is of greater intensity than would be provided by brief or extended brief interventions" and that "the current services available in England have difficulty providing the level of psychosocial interventions recommended in NICE clinical guideline 115". It is stated 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" and "concluded that the clinical effectiveness evidence based on the comparison with BRENDA was relevant to clinical practice in England".

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Conflicts of interest Marsha Morgan has received payment from Lundbeck for attending an advisory board. Jez Thompson received sponsorship by the Substance Misuse Management in General Practice (SMMGP) network to undertake an advanced certificate course in the management of alcohol problems in primary care. The funds for this had been provided to SMMGP by Lundbeck. Matt Stevenson, Abdullah Pandor, John Stevens, Andrew Rawdin and Peter Rice declare no financial conflict of interest.

Contributions made by each author Matt Stevenson and Andrew Rawdin critiqued the mathematical model provided and the cost-effectiveness analyses submitted by the manufacturer. Abdullah Pandor critiqued the clinical effectiveness data reported by the manufacturer. John Stevens critiqued the statistical analyses undertaken by the manufacturer. Marsha Morgan, Peter Rice, and Jez Thompson provided clinical advice to the ERG throughout the project. All authors were involved in drafting and commenting on the final document. Matt Stevenson acts as the guarantor of the manuscript.

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