NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal determination

Nalmefene for reducing alcohol consumption in people with alcohol dependence

This guidance was developed using the single technology appraisal (STA) process

1 Guidance

1.1 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 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, and
- who do not require immediate detoxification.

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 level 2 weeks after initial assessment.

2 The technology

2.1 Nalmefene (Selincro, Lundbeck) is an opioid receptor modulator, which exhibits antagonist activity at the mu and delta opioid receptors, and

partial agonist activity at the kappa opioid receptors. Nalmefene has a marketing authorisation in the UK for 'the reduction of alcohol consumption in adult patients with alcohol dependence who have a high drinking risk level without physical withdrawal symptoms and who do not require immediate detoxification'. The summary of product characteristics states that a high drinking risk level is defined as alcohol consumption of more than 60 g (7.5 units) per day for men and more than 40 g (5 units) per day for women, according to the World Health Organization's drinking risk levels.

2.2 The marketing authorisation also states that 'nalmefene should only be prescribed in conjunction with continuous psychosocial support focused on treatment adherence and reducing alcohol consumption. It should only be started in patients who continue to have a high drinking risk level 2 weeks after initial assessment'.

2.3 The summary of product characteristics lists the following adverse reactions for nalmefene: nausea, dizziness, insomnia and headaches. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.4 Nalmefene is available as an 18 mg film-coated tablet and is priced at £42.42 for a pack of 14 tablets or £84.84 for a packet of 28 (excluding VAT; 'British national formulary' [BNF], online April 2014). It is taken orally at a maximum dose of 1 tablet daily on an 'as-needed' basis. Costs may vary in different settings because of negotiated procurement discounts.

3 The company's submission

The Appraisal Committee (section 8) considered evidence submitted by the company of nalmefene and a review of this submission by the Evidence Review Group (ERG; section 9).

Clinical effectiveness

Nalmefene compared with psychological intervention

3.1 The company identified 3 randomised controlled trials (ESENSE1, ESENSE2 and SENSE) in adults with alcohol dependence, comparing 18 mg nalmefene (on an as-needed basis) plus psychosocial support with placebo plus psychosocial support. ESENSE1 (n=604) and ESENSE2 (n=718) were identical efficacy studies with a follow-up period of 24 weeks. SENSE (n=675) was primarily designed to collect safety data for up to 12 months on nalmefene, but after the study had started the protocol was amended to include efficacy analyses. SENSE had a follow-up period of 12 months.

3.2 Psychosocial support (in the form of BRENDA), focusing on treatment adherence and reduction of alcohol consumption, was provided to all treatment groups in the 3 studies. The first part comprised a biopsychosocial evaluation, followed by sharing the results with the patient. The next stage involved expressing empathy for the patient and together identifying their needs, providing direct advice to the patient to meet those needs, assessing patient reaction to advice and adjusting the treatment plan as needed. All sessions were provided by trained professionals and were delivered at weekly intervals for the first 2 weeks and then monthly. Sessions lasted for 15–30 minutes except for the first longer session, which was 30–40 minutes.

3.3 Alcohol dependence was diagnosed using the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR). To be included in the studies, patients must have had 14 or fewer days of abstinence in the 28 days preceding the screening visit, and have an average daily alcohol consumption of medium risk or higher: equivalent to more than 40 g per day (equivalent to more than 5 units) for men and more than 20 g per day (equivalent to more than 2.5 units) for women. Patients had at least 6 heavy drinking days in the 28 days prior to enrolment. A heavy drinking

day was defined, in line with the World Health Organization classification of drinking risk levels, as alcohol consumption of more than 60 g per day (equivalent to more than 7.5 units) for men and more than 40 g per day (equivalent to more than 5 units) for women. People with severe medical comorbidities were excluded from all 3 studies, and those with severe psychiatric comorbidities were excluded from the 2 ESENSE trials. The 3 studies were conducted across different regions of Europe. In total, there were 156 sites; 5 sites in the UK were included in the SENSE trial.

3.4 The ESENSE trials contained 4 study periods. The first was a 1- to 2-week screening period, after which all patients were randomised 1:1 to either the nalmefene plus BRENDA group or placebo plus BRENDA group for 24 weeks. Patients were then instructed to take 1 tablet (the maximum daily dose) on an 'as-needed' basis, preferably 1–2 hours before they perceived a risk of drinking. If the patients started to drink without taking a tablet, they were advised to take a tablet as soon as possible. The patients who completed the 24-week trial entered a 4-week, double-blind, run-out period to evaluate any treatment discontinuation effects. Those who had been initially randomised to nalmefene were re-randomised to receive either nalmefene or placebo, and patients originally in the placebo group continued on placebo. A safety follow-up visit was scheduled for 4 weeks after completion of the run-out period or after withdrawal from the study.

3.5 Similar to the ESENSE studies, the SENSE study also began with a 1- to 2-week screening period, after which patients were randomised 3:1 to receive 52 weeks of as-needed treatment with nalmefene plus BRENDA or placebo plus BRENDA. A safety follow-up period was scheduled for 4 weeks after completion of the study or after withdrawal from the study.

3.6 The primary outcomes in ESENSE1 and ESENSE2 measured changes from baseline in the number of heavy drinking days per month and total alcohol consumption at month 6. The company highlighted that the

primary end points of number of heavy drinking days and total alcohol consumption were in accordance with the recommendations in the European Medicines Agency guideline on the development of medicinal products for the treatment of alcohol dependence. Total alcohol consumption was defined as mean daily alcohol consumption in grams per day, over a month (28 days). Patients self-reported their daily alcohol consumption using the timeline follow-back method at monthly intervals. This provided retrospective estimates of the number of standard drinks consumed each day in the previous month, which were subsequently converted into grams of alcohol per day. Secondary outcomes included the effect of nalmefene on: proportion of people whose alcohol dependence responded to treatment based on different drinking measures, alcohol dependence symptoms and clinical status, liver function and other clinical safety laboratory tests, pharmaco-economic outcomes, treatment withdrawal effects after 24 weeks, safety and tolerability of nalmefene and quality-of-life measures (SF-36 and EQ-5D).

3.7 Similar to ESENSE1 and ESENSE2, the primary outcomes for the SENSE study were change from baseline in the number of heavy drinking days per month and total alcohol consumption at month 6. These outcomes were added as an amendment to the protocol while the study was ongoing. No protocol amendments were made to outcomes to assess the safety and tolerability of nalmefene.

3.8 In ESENSE1 and ESENSE2, approximately 78% of all patients enrolled had a high or very high drinking risk level at baseline. In SENSE, 52% of the enrolled patients had a high or very high drinking risk level at baseline. In ESENSE1, ESENSE2 and SENSE, 74%, 57% and 52% respectively continued drinking at this level at randomisation. After an agreement with the Scientific Advisory Group to the European Medicines Agency, the company performed a post hoc analysis in the subgroup of patients in the 3 studies who had a high or very high drinking risk level both at baseline and at randomisation. The company stated that the Scientific Advisory

Group recognised the validity of the post hoc subgroup analyses and that these analyses form the basis of the marketing authorisation for nalmefene.

3.9 Results of the post hoc analyses in the licensed population (that is, people who had a high or very high drinking risk level at baseline and maintained such a level at randomisation) showed that there were greater reductions in the number of heavy drinking days and total alcohol consumption in patients treated with nalmefene plus BRENDA, than with placebo plus BRENDA. The treatment difference in the changes from baseline to 6 months in the number of heavy drinking days, using mixed model repeated measures analysis, was −3.7 days per month (95% confidence interval [CI] −5.9 to −1.5, p=0.001) in ESENSE1, and −2.7 days per month (95% CI −5.0 to −0.3, p=0.025) in ESENSE2. The treatment difference in the changes from baseline to 6 months in total alcohol consumption was −18.3 g per day (95% CI −26.9 to −9.7, p<0.001) in ESENSE1, and −10.3 g per day (95% CI −20.2 to −0.5, p=0.040) in ESENSE2. In the SENSE study, the treatment difference in the changes from baseline to 6 months in the number of heavy drinking days was −2.6 days per month (95% CI −5.5 to 0.2, p=0.071) at 6 months, and −3.6 days per month (95% CI −6.5 to −0.7, p=0.016) at month 13. The difference in total alcohol consumption at month 6 was −15.3 g per day (95% CI −29.1 to −1.5, p=0.031) and at month 13 was −17.3 g per day (95% CI −30.9 to −3.8, p=0.013).

3.10 The company did not perform a meta-analysis of the efficacy data for the ESENSE1, ESENSE2 and SENSE studies but pooled the primary outcomes, the change from baseline to month 6 in monthly heavy drinking days, and total alcohol consumption from ESENSE1 and ESENSE2. In the ESENSE1 and ESENSE2 studies there were 23 heavy drinking days per month at baseline in the nalmefene plus BRENDA group with a reduction to 10 heavy drinking days per month at month 6 (a reduction of 55%). In the placebo plus BRENDA group there were 22 heavy drinking

days per month at baseline with a reduction to 13 heavy drinking days per month at month 6 (a reduction of 42%). At 6 months the number of heavy drinking days had been reduced by 3.01 days per month (95% CI −4.36 to −1.66, p<0.0001) and total alcohol consumption had been reduced by 14.22g per day (95% CI −19.96 to −8.47, p<0.0001). In the ESENSE1 and ESENSE2 studies there was a total alcohol consumption of 107.7 g per day in the nalmefene plus BRENDA group, which reduced to 49.0 g per day at month 6 (a reduction of 61%). In the placebo plus BRENDA group there was a total alcohol consumption of 103.3 g per day, which reduced to 51.9 g per day at month 6 (a reduction of 50%). The odds ratio for the pooled response of drinking risk level for the ESENSE1 and ESENSE2 trials was 1.87 (95% CI 1.35 to 2.59, p<0.001).

3.11 The company reported the results for a number of secondary outcomes in the 3 nalmefene studies. Secondary outcomes included response at month 6 (response of drinking risk level defined as a downward shift from baseline in drinking risk level by 2 risk categories). The odds ratio for nalmefene for response of drinking risk level was 2.15 (95% CI 1.38 to 3.36, p<0.001) in the ESENSE1 study and 1.59 (95% CI 0.98 to 2.59, p=0.062) in the ESENSE2 study. In ESENSE1 and ESENSE2, the EQ-5D health state and utility index score in the licensed population increased more from baseline to month 6 in the nalmefene plus BRENDA group than in the placebo plus BRENDA group. This was statistically significantly in favour of nalmefene for the health state score in ESENSE1 only. Pooled analysis of the EQ-5D (a quality of life questionnaire) results in ESENSE1 and ESENSE2 in the licensed population produced a mean change from baseline, for the health state score and the utility index score, of 3.46 points (p=0.0124) for the health state score and 0.03 points (p=0.0445) for the utility index score. The EQ-5D health state and utility index score in the licensed population increased more from baseline to month 6 in the nalmefene group than in the placebo group with a mean change in utility index score from baseline to month 6 of 0.03±0.02 (95% CI 0.00 to 0.06,

p=0.0445) and a mean change in health state score from baseline to month 6 of 3.46±1.38 (95% CI 0.75 to 6.17, p=0.0124).

Nalmefene compared with naltrexone

3.12 Because there were no direct head-to-head studies comparing nalmefene plus BRENDA with naltrexone (comparator) plus psychosocial intervention, the company investigated whether a network meta-analysis or indirect comparison could be conducted. The company carried out a systematic review to identify studies evaluating nalmefene and naltrexone for the reduction of alcohol consumption in people who were actively drinking and had alcohol dependence. The review identified 3 randomised controlled studies that compared oral naltrexone (50 mg per day) plus psychosocial intervention, with placebo plus psychosocial intervention in actively drinking adults with alcohol dependence. The company stated that all the studies had limitations in the data reported, meaning that an indirect comparison could not be performed. These differences included study design, inclusion and exclusion criteria, study objective and end points as well as a lack of reporting of data from the naltrexone studies.

BRENDA (psychosocial support in ESENSE1, ESENSE2 and SENSE) compared with other types of psychological interventions

3.13 To determine which types of psychosocial intervention should be included in the systematic review, the company carried out a survey of 20 primary care practices and experts and concluded that the following types of psychosocial intervention should be incorporated: cognitive behavioural therapies, behavioural therapies, social network and environment therapies, brief interventions and motivational enhancement therapy.

3.14 The company carried out a literature search and identified 7 studies on psychosocial intervention that met the inclusion criteria and which the company added to the 43 studies identified in Alcohol dependence and harmful alcohol use (NICE clinical guideline 115). The company did not carry out a meta-analysis of these studies (no explicit reasons were

provided in the company's submission) but it did provide a summary of the absolute reductions in drinking that were provided in the psychosocial intervention trials. These trials showed that absolute reduction in total alcohol consumption from these studies ranged from 9.3–50.7 g per day, with a median value of 18.3 g per day (range of follow-up time: 6–12 months). For the absolute reduction in number of monthly heavy drinking days, the range was 1.3–19, with a median value of 5.7 days (range of follow-up time: 3–12 months). In the nalmefene studies, the absolute reduction in total alcohol consumption in the nalmefene plus BRENDA group ranged from 58.3–70.4 g per day, whereas in the placebo plus BRENDA group, the absolute reduction ranged from 40.0–60.1 g per day. The absolute reduction in the number of monthly heavy drinking days in the nalmefene plus BRENDA group ranged from 11.6–12.9 days, whereas in the placebo plus BRENDA group the absolute reduction ranged from 8.0–10.2 days (range of follow-up time: 6–12 months).

3.15 The frequency of treatment-emergent adverse events was recorded for all 3 nalmefene trials for both the total and licensed population. The percentage of adverse events was slightly higher in the licensed population than in the total population. The adverse events observed with the highest incidences in the nalmefene group as compared with the placebo group were nausea, dizziness, insomnia and headache. The incidence of nausea (22%) and dizziness (18%) were high in the first month of treatment but decreased to approximately 1–2% in subsequent months. Treatment-emergent psychiatric events that included confusion, abnormal thinking and hallucinations were approximately 3 times more common with nalmefene, with an incidence of 2.9%.

Cost effectiveness

3.16 The company developed a de novo analysis to estimate the cost effectiveness of as needed nalmefene plus psychosocial support compared with psychosocial support alone for treating alcohol dependence. The company used a Markov model, which consisted of a

short-term model (1 year based on the nalmefene studies) with 1 month cycles, and a long-term model (up to 5 years using extrapolated trial results) with 1 year cycles. The model with 1 month cycles aimed to take account of treatment efficacy and patient adherence, observed treatment discontinuation, incidence of alcohol-attributed harmful events and deaths. It also reduced the number of assumptions and uncertainties needed by the company. The 1 month cycle length was used to align with the patient follow-up in the nalmefene studies (number of heavy drinking days and total alcohol consumption over 28 days). Half-cycle correction was not incorporated because the company considered these to be negligible, because the initial cycles were 1 month long. The model was developed based on the nalmefene studies that used BRENDA as the psychosocial support.

3.17 The population in the model consisted of a cohort with alcohol dependence and defined drinking levels according to the World Health Organization's definition of drinking-risk levels (see table 1). In accordance with the pooled data from ESENSE1, ESENSE2 and the SENSE studies, the company assumed that on entry to the model, 57.5% of those patients who met the criteria specified in the marketing authorisation for nalmefene, would be in the very high risk drinking level and 42.5% would be in the high risk drinking level.

Table 1 World Health Organization definition of drinking risk levels

Drinking risk level (applies to a single day)	Total consumption (g/day)	
	Men	Women
Very high risk	>100	>60
High risk	>60–100	>40–60
Medium risk	>40–60	>20–40
Low risk	1–40	1–20
Abstinent	0	0

3.18 The short-term time horizon of 1 year contained 5 drinking level health states as shown in table 1. Patients entered the model in either the high or very high drinking level state in line with the marketing authorisation for

nalmefene. After the first year, 3 yearly health states were considered: controlled drinking, medium risk drinking, and high or very high risk drinking. Patients in the controlled drinking health state were assumed to be of a low risk drinking level or abstinent after 12 months and therefore these patients stopped all treatments.

3.19 To account for the possibility that patients with controlled drinking may become heavy drinkers again, 19% were modelled to relapse at the end of the year and due to have a second round of treatment. Patients who relapsed returned to the same treatment in which they were initially successful in controlling their alcohol intake. The proportion of patients who relapsed was also distributed among the drinking levels in the same way as the initial patient cohort in the model. The same transition probabilities were also applied. It was assumed that treatment was effective in patients in the medium risk drinking level group after 12 months, and patients continued on treatment but this only applied to approximately 10% of patients in the model. These patients could transition to either controlled drinking or high or very high risk drinking level, leading to a second-line treatment option. After 12 months, it was presumed that treatment was not effective in patients in the high or very high risk drinking group and their current treatment was stopped. They were modelled to change treatment strategy to an abstinence-orientated or second-line approach, which would include assisted alcohol withdrawal followed by acamprosate or oral naltrexone plus psychosocial intervention, to prevent relapse.

3.20 Transition probabilities for patients changing drinking state in the first year were obtained from pooled data from the ESENSE1, ESENSE2 and SENSE studies. Transition probabilities for the subsequent years were obtained from different sources, depending on the drinking risk level. The abstinent or low drinking risk levels were based on data reported by Taylor et al. (1985), with the transition probabilities for those in the

medium drinking risk level calculated from the last 6 months of the SENSE study.

3.21 The risk of a patient experiencing a serious or temporary harmful event was related to their World Health Organization drinking risk level. The serious harmful events included by the company were based firstly on those events that were costly to the healthcare system and had a strong evidence base. The company also modelled temporary events using tunnel states including costs and quality-adjusted life year (QALY) decrements but no long-term effects were accounted for when the person survived the tunnel state. Temporary events comprised of lower respiratory tract infections, transport-related injuries and injuries not related to transport. Patients who experienced a serious event stayed in that state for the remaining duration of the model. Patients who experienced a temporary event stayed in a tunnel health state for 1 month before returning to the pre-tunnel health state. In a tunnel state, the proportion of patients passing through the state (or event) acquired costs and an immediate decrement in utility, in addition to other costs (alcohol treatment costs) and utilities incurred by the drinking level health states. However, the state or event will not produce any long-term effects as long as the patient survives the tunnel state.

3.22 To take account of the risks of crime in the first year of treatment, the company applied relative risks for each drinking risk level to an underlying general population value, which is assumed to be those patients that are abstinent. The company assumed a number of probabilities of committing crime based on gender in the first year.

3.23 The company's model allowed patients to move from any health state to the death state over the time horizon. Patients could die either from alcohol-attributed harmful events or all-cause mortality.

3.24 The model also incorporated risks of dropping out because of harmful events from nalmefene or other reasons. This was based on data from the

3 pooled nalmefene clinical trials in the model. An adverse event could cause the patient to change or stop their treatment, depending on the treatment and the source of the adverse event. If a patient dropped out because of nalmefene-related adverse events, they stayed in the nalmefene treatment arm but their treatment changed to psychosocial support only. Patients who changed treatment because of nalmefene-related adverse events transitioned to their corresponding drinking level for the psychosocial support treatment. For both the nalmefene plus psychosocial support treatment and the psychosocial support alone, patients who dropped out because of other reasons had their treatment changed to 'no treatment' and transitioned immediately to high or very high World Health Organization drinking risk level with the same distribution as at entry into the model.

3.25 A number of cost parameters were used in the model, with the cost of a visit to the GP or expert care being the same for both nalmefene plus psychosocial support and psychosocial support alone. For both these groups, the proportion of patients receiving treatment at a GP practice and at expert level was set at 75% and 25% respectively.

3.26 In the model, the costs of second-line treatment with naltrexone or acamprosate were taken from NICE clinical guideline 115. The second-line treatment for assisted withdrawal using naltrexone or acamprosate had several costs attached, depending on the location of treatment: home-based assisted withdrawal (£596), secondary care outpatient-assisted withdrawal (£606) or secondary care inpatient-assisted withdrawal (£4145). The company then used a weighted average of £1044 per patient having medically assisted withdrawal. The model also took into account societal costs related to both crime and productivity as specified in the remit to NICE from the Department of Health. The inclusion of a societal perspective was taken account of in scenario analyses and was not included in the company's base case.

3.27 Utility weights were obtained from the EQ-5D questionnaire, used to assess patients' health-related quality of life in the 3 nalmefene trials. The EQ-5D data were used to model the effect of a reduction in alcohol consumption. The results from the 3 trials were pooled to estimate utility values for the cost-effectiveness model (see section 3.11 for results).

3.28 The company's base-case results showed that nalmefene plus psychosocial support dominated psychosocial support alone (that is, it is more effective and less costly). The company carried out a number of sensitivity analyses. The parameters that had the most effect on the cost effectiveness results were the number of medical visits per month (for both treatments), the proportion of people having treatment following relapse, the utility values used and the cost of nalmefene. Nalmefene plus psychosocial support still dominated when all parameters were varied, except for when the number of medical visits per month was doubled. When applying the upper bound for this parameter, the incremental cost-effectiveness ratio (ICER) increased to £6274 per QALY gained.

3.29 The company also tested 8 different scenarios observing the impact of varying the time horizon, perspective on cost, assuming nalmefene intake on every day that the patient was in the model, source of utility data used and removing the second-line treatment option (results in brackets after each scenario).

- Scenario 1: Time horizon reduced to 1 year (ICER was £24,684 per QALY gained for nalmefene plus psychosocial support compared with psychosocial support).
- Scenario 2: Societal perspective included (nalmefene plus psychosocial support continued to dominate psychosocial support).
- Scenario 3: Time horizon reduced to 1 year and societal perspective included (nalmefene plus psychosocial support continued to dominate psychosocial support).

- Scenario 4: Nalmefene intake assumed to be every day rather than as needed (ICER was £289 per QALY gained for nalmefene plus psychosocial support compared with psychosocial support).
- Scenario 5: No second-line treatment options are allowed (ICER was £5090 per QALY gained for nalmefene plus psychosocial support compared with psychosocial support).
- Scenario 6: Using utility values from the STREAM study (nalmefene plus psychosocial support continued to dominate psychosocial support).
- Scenario 7: A threshold analysis increasing the treatment effect of psychosocial support relative to nalmefene plus psychosocial support to identify the level of efficacy needed to have an ICER of £20,000 and of £30,000 per QALY gained.
- Scenario 8: An assumption that psychosocial support was associated with zero costs (£8088 cost per QALY gained for nalmefene plus psychosocial support compared with psychosocial support).

3.30 After a clarification request, the company corrected a minor error in the model and presented 2 further scenarios (termed scenarios 9 and 10 by the ERG). Scenario 9 provided an ICER for the use of psychosocial intervention as suggested by NICE clinical guideline 115, with 1 session of psychosocial intervention lasting 60 minutes per week for 12 weeks. Scenario 9A increased the costs of psychosocial support in the psychosocial support alone arm, whereas scenario 9B assumed the cost increase for psychosocial support applied to both nalmefene plus psychosocial support arm and psychosocial support alone arm. In both situations (9A and 9B), nalmefene plus psychosocial support dominated psychosocial support alone. Scenario 10 assessed alternative assumptions for the treatment pathway of patients at a medium risk level after 12 months. Three scenarios were explored: the first assumed that patients relapse after 12 months to high or very high drinking risk level; the second assumed that treatment was effective and was modelled in

line with other patients in whom treatment was effective; the third scenario assumed that treatment was not effective in patients in the nalmefene plus psychosocial support arm but that it was for patients in the psychosocial support alone arm. For the first 2 scenarios, nalmefene plus psychosocial support still dominated psychosocial support alone, whereas for the third scenario the ICER was £6280 per QALY gained when comparing nalmefene plus psychosocial support with psychosocial support alone.

Evidence Review Group's comments

3.31 The ERG commented that the company had carried out a comprehensive systematic review and all relevant studies for nalmefene plus psychosocial support were included. It was unsure if all relevant naltrexone data had been included. The ERG also commented that the company's model was generally well constructed and had few errors.

3.32 The ERG indicated that the post hoc subgroup analyses of patients who had high or very high drinking risk level in the 3 nalmefene studies may cause the efficacy and safety data to be less robust because they were not powered for this analysis. The robustness may also be affected by the high dropout rates in the nalmefene trials. The company carried out sensitivity analyses to account for the missing data but there were some inconsistencies as to whether statistical significance was achieved or not. The ERG also indicated that patient self-reporting of alcohol intake could bias the results.

3.33 The ERG indicated that the uncertainties in the clinical evidence related to the types and frequencies of psychosocial intervention, along with its treatment duration and generalisability to England. Psychosocial support in the form of BRENDA was used in the nalmefene trials but was delivered at different intervals to the psychosocial intervention (including behavioural therapies, cognitive behavioural therapy and behavioural couples therapies) recommended in NICE clinical guideline 115. 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.

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 company 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 company 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.

3.35 The ERG noted that naltrexone was not formally modelled as a comparator in the economic analysis even though it was included in the final scope issued by NICE. The model assumed that if patients stopped nalmefene treatment because of adverse events, they would switch to psychosocial support alone, but it did not account for switching to naltrexone. The ERG commented that it was unsure whether this assumption could be favourable or unfavourable to nalmefene.

3.36 The ERG stated that its clinical advisers did not agree with the assumption that people would remain on treatment (regardless of drinking level) for the full year. The ERG commented that its clinical advisers believed that GPs would not let patients drink at very high risk levels for more than 6 months without recommending intensification of psychosocial

intervention and additional expert input, and that 3 months might be a more likely cut-off point.

Evidence Review Group's exploratory analyses

3.37 The ERG formulated 4 comparisons in its exploratory analysis (see table 2).

Table 2 The 4 comparisons formulated by the Evidence Review Group

Comparison	Definition
Comparison 1	The analysis of the cost effectiveness of adding nalmefene to a psychosocial intervention of lower intensity than recommended in NICE clinical guideline 115.
Comparison 2	Threshold analyses that estimates the reduction in the benefit associated with nalmefene necessary to reach cost per quality-adjusted life years (QALYs) of £20,000 and £30,000.
Comparison 3	The company 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. Delayed use of nalmefene would be aligned with the recommendation for pharmacotherapy in NICE clinical guideline 115, although this guideline was written before nalmefene was licensed.
Comparison 4	The company did not comment on the likely cost effectiveness of nalmefene use (delayed or immediate) with the use of off-label naltrexone, following informed consent being obtained, as recommended in NICE clinical guideline 115.

3.38 For comparison 1, the ERG carried out a number of exploratory analyses including:

- Analysis 1: Impact of patients withdrawing from nalmefene because of adverse events also withdrawing from psychosocial support – 2 scenarios were run, the first assumed that all patients withdrawing from nalmefene also withdrew from psychosocial support, and the second assumed that 50% of the patients also withdrew from psychosocial support.
- Analysis 2: 50% of patients received outpatient medically assisted withdrawal and 50% had this treatment at home.

- Analysis 3: The costs for serious and temporary events were zero and the utility was the same as the very high risk level, although the ERG did not deem this plausible.
- Analysis 4: The cost of an expert psychosocial support appointment was £119 rather than £94, according to more recent data.
- Analysis 5: The utility for patients on nalmefene plus psychosocial support and for psychosocial support alone were equal in the first year, although the ERG did not deem this plausible.

3.39 The ERG's base case included assumptions 1, 2 and 5, with the additional assumption that 50% of people withdrawing from nalmefene would also withdraw from psychosocial support treatment. In the ERG base case, nalmefene plus psychosocial support still dominated psychosocial support alone. The ERG carried out a second analysis using their base case assumption but also presumed no second-line treatment options were allowed and the ICER was £5166 per QALY gained when comparing nalmefene plus psychosocial support with psychosocial support alone. Although the ERG was critical of the fact that the company did not conduct a half-cycle correction, the model was not adapted by the ERG to allow this for 2 reasons: the first was the time needed to carry out this adaptation and the second because after the first year (in which monthly cycles were used), there was no differential efficacy between the 2 arms apart from people drinking at medium drink risk levels. Also, any potential inaccuracy was relatively small compared with the uncertainty explored in comparisons 2 and 3.

3.40 For comparison 2, the ERG suggested that it was unlikely for people at medium risk drinking level to have treatment indefinitely and assumed in comparison 1 that these people would relapse to high and very high risk levels. The ERG was unable to carry out a threshold analysis altering the variable treatment options because this part of the model was not functioning, and also given that the impact in the ICER was small, the ERG left the assumption as it was. The threshold analysis carried out by

the company in scenario 7 was re-assessed in the ERG's comparison 2 (with the exception that those at a medium risk drinking level were assumed to remain on treatment). The results produced by the ERG were similar to the company's results. If the efficacy of nalmefene and psychosocial support compared with psychosocial support alone were reduced by 62.8%, then the ICER would become £20,000 per QALY gained. The reduction would have to be 71.5% for the ICER to reach £30,000 per QALY gained. When additional factors accounting for the potential cost of crime and loss of productivity were considered, the efficacy of nalmefene and psychosocial support compared with psychosocial support alone would need to be reduced by 80.4% and 83.1% for the ICER to be £20,000 and £30,000 per QALY gained respectively.

3.41 For comparison 3, the ERG highlighted that there were few data to assess the cost effectiveness of nalmefene with psychosocial intervention when using the psychosocial intervention as described in NICE clinical guideline 115. The time point at which psychosocial intervention alone was not successful was also unknown but the nalmefene trials indicated that when patients were treated with BRENDA alone, approximately 20% were either abstinent or of low risk drinking level at month 3. The ERG suggested a greater response may be seen with higher-intensity psychosocial intervention and that the costs of nalmefene can be saved without incurring health losses particularly if nalmefene use was delayed. The ERG did caution that there would be uncertainty about the efficacy of nalmefene in patients whose alcohol dependence had not responded to psychosocial support alone.

3.42 For comparison 4, again the ERG suggested there were few data available and therefore did not feel comfortable estimating an ICER for this comparison.

3.43 Full details of all the evidence are in the company's submission and the ERG report.

4 Consideration of the evidence

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of nalmefene, having considered evidence on the nature of reducing alcohol consumption in people with alcohol dependence and the value placed on the benefits of nalmefene by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

4.1 The Committee considered the clinical need for treatment in people with alcohol dependence and who have a high drinking risk level. It heard from a patient expert about the impact of alcohol dependency on both the patient and their family. The patient experts explained that the aim of treatment is to reduce the impact of symptoms on quality of life, including physical, mental and financial constraints for the patient and their family. The clinical experts stated that reducing alcohol intake also reduces the extent of liver disease in patients. The patient experts also explained that the availability of any extra interventions to treat alcohol dependency would be welcomed, because the currently available treatments are not always successful.The Committee acknowledged the demands that living with alcohol dependency can have on the patient and their family and accepted that an additional treatment option for these patients is important.

4.2 The Committee discussed the current clinical management of alcohol consumption in people with alcohol dependency who have a high drinking risk level, without physical withdrawal symptoms and who do not require immediate detoxification, including the most appropriate comparator for nalmefene. The Committee was aware that Alcohol use disorders (NICE clinical guideline 115) recommends that moderation of drinking, rather than abstinence from alcohol, may be appropriate for people with mild

dependence without significant comorbidity and with adequate social support. It heard from the clinical experts that psychosocial intervention in the form of brief or extended brief interventions was the standard first-line treatment in England for these people. The Committee understood 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. It noted that both the duration and frequency of these interventions were shorter than that recommended in the guideline and that the provision of psychosocial interventions differs throughout England. The Committee was aware that naltrexone was also listed as a comparator in the final scope for this appraisal, despite it not having a marketing authorisation in the UK for this indication. However, the clinical experts explained 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 noted that during consultation, some consultees indicated that naltrexone is sometimes used in practice to treat mild alcohol dependency because it is pharmacologically similar to nalmefene. The Committee heard from the clinical experts that nalmefene plus psychosocial support is an important addition to the treatment pathway because it is the first pharmacological intervention that is specifically for alcohol reduction rather than abstinence. The Committee concluded that psychosocial intervention in the form of brief or extended brief intervention is a valid comparator for nalmefene plus psychosocial support and the most appropriate comparator for this appraisal.

4.3 The Committee considered how nalmefene will be prescribed in clinical practice, noting that the marketing authorisation states that ‘nalmefene should only be prescribed in conjunction with continuous psychosocial support’. The Committee heard 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 expert. However, during consultation, some consultees suggested that expert alcohol services in secondary care were still providing psychosocial interventions for patients who do not require pharmacological assistance. The patient experts explained that providing nalmefene treatment in primary care could reduce the stigma sometimes associated with expert treatment, and that families may also feel empowered to help people continue with treatment. The Committee was aware that for harmful drinkers and people with mild alcohol dependence, NICE clinical guideline 115 recommends that psychosocial intervention (including behavioural therapies, cognitive behavioural therapy and behavioural couples therapies) should typically consist of 60 minute weekly sessions over a 12week period, and be delivered by appropriately trained and competent staff. The Committee was also aware that the psychosocial intervention in the guideline is of greater intensity than would be provided by brief or extended brief interventions. The Committee heard from the clinical experts that the current services available in England have difficulty providing the level of psychosocial interventions recommended in NICE clinical guideline 115 . Other comments received during consultation suggested that GPs would need further training to provide psychosocial support to patients and that brief or extended brief intervention as provided by GPs, is not at the intensity of BRENDA used in the trials. 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, it was aware that making specific recommendations about the setting for prescribing nalmefene was outside the scope of a technology appraisal.

Clinical effectiveness

4.4 The Committee considered the evidence on the clinical effectiveness of nalmefene plus psychosocial support, noting that the evidence was

derived from the ESENSE1, ESENSE 2 and SENSE studies. It discussed whether the population in the 3 studies reflects those seen in clinical practice in England, and whether it could allow clinicians to determine the population eligible for nalmefene. 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 last 28 days, and 14 or fewer abstinent days in the 4 weeks before the screening visit. It heard from the clinical experts that the inclusion criteria reflected the definition in NICE clinical guideline 115 for mild alcohol dependence and the World Health Organization's classification of drinking risk levels.The Committee noted that the 2 ESENSE studies excluded people with severe psychiatric conditions or severe medical comorbidities, but noted the company's consultation response explaining that at the UK sites of the SENSE trial, nalmefene was given to patients with stable psychiatric comorbidities and who were taking multiple medications. It also noted that none of the sites in the ESENSE trials was in the UK, and that only 5 sites in the SENSE trial were UK-based. The Committee was aware that both the company and the Evidence Review Group (ERG) had commented that many people who have alcohol dependence also have medical conditions or psychiatric conditions. The Committee was also aware that the clinical experts agreed with this view. The Committee concluded that the baseline characteristics of the populations in the 3 studies were not wholly generalisable to clinical practice in England, but provided sufficient evidence for clinicians to determine the appropriate patient population for treatment with nalmefene plus psychosocial support, with the psychosocial support focusing on treatment adherence and reducing alcohol consumption.

4.5 The Committee discussed the psychosocial support used both in conjunction with and as a comparator to nalmefene in the ESENSE1, ESENSE2 and SENSE studies. It was aware that the psychosocial support provided in the studies was in the form of BRENDA (see section 3.1), which is not currently used in clinical practice in England, although it is used in clinical trials. The Committee considered if BRENDA, as administered in the clinical trials, is applicable to clinical practice in England. It was aware that NICE clinical guideline 115 specifies the type and frequency of psychosocial intervention that should be offered to people with mild alcohol dependence who wish to reduce their alcohol consumption, and that both the intervention and comparator in the final scope issued by NICE specified psychological intervention 'as defined in NICE clinical guideline 115'. The Committee heard from the clinical experts that BRENDA was delivered at different intervals and intensity to both the psychosocial intervention as described in NICE clinical guideline 115 and that used in clinical practice in England. However, it heard from the clinical experts 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. The Committee accepted that BRENDA, as described in the 3 nalmefene studies, closely resembled current established practice. It concluded that the clinical effectiveness evidence based on the comparison with BRENDA was relevant to clinical practice in England.

4.6 The Committee considered the clinical-effectiveness results of the 3 nalmefene studies. It agreed that it should only consider the post hoc subgroup analyses carried out on trial patients in the 3 nalmefene studies with a high or very high drinking risk level at baseline who maintained such a level at randomisation because these analyses formed the basis of the licensed population in the marketing authorisation for nalmefene. The Committee was aware that the subgroup analyses had not been pre-specified but had been performed because 18% (ESENSE1), 33%

(ESENSE2) and 25% (SENSE) of patients reduced drinking between screening study visits and randomisation, therefore leaving little scope for additional improvement. The Committee noted the ERG's concerns that the subgroup efficacy data may be less robust because none of the studies were powered for this analysis and initial randomisation may have been lost with the high dropout rate possibly affecting the results. It was also aware that the Scientific Advisory Group to 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. The Committee accepted that the post hoc subgroup analyses were sufficiently robust to use in its decision-making. It noted that the results from the post hoc subgroup analyses suggested that people in the nalmefene plus BRENDA group had fewer heavy drinking days per month and total alcohol consumption per day compared with those who received placebo plus BRENDA. However, 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 to the psychosocial support (BRENDA). The Committee heard from the clinical experts that both the number of heavy drinking days and total alcohol consumption are clinically relevant outcome measures and that although the reduction in these outcomes appear modest, they are clinically significant. 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 for these analyses (see section 3.8).

4.7 The Committee noted that there were no trials directly comparing nalmefene plus psychosocial support with naltrexone plus psychosocial intervention, and the company had not presented an indirect comparison of the 2 treatments. The Committee accepted the rationale provided by

the company and that the ERG had agreed it would be inappropriate to carry out an indirect comparison given the limitations of the naltrexone studies identified by the company. The Committee was aware that naltrexone plus psychosocial intervention is recommended in NICE clinical guideline 115 (although oral naltrexone does not have UK marketing authorisation for this indication) for people whose alcohol dependence did not respond to psychosocial intervention, or those who have specifically requested a pharmacological intervention, and that it was included as a comparator in the final scope issued by NICE. 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 noted that consultation comments from a professional group and patient and carer group suggested a comparison between naltrexone and nalmefene would be helpful, because some patients are being treated with naltrexone in a similar way to the nalmefene licence. It considered whether an indirect comparison should have been carried out (albeit an imperfect one) as it was included in the final scope issued by NICE. The Committee had heard from the clinical experts 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.

4.8 The Committee considered the health-related quality of life benefits associated with nalmefene plus BRENDA. The Committee noted that the company had collected health-related quality of life data as measured by the EQ-5D and SF-36 in all 3 nalmefene trials. The Committee was aware that the reference case outlined in NICE's Guide to the methods of technology appraisal 2013 states that EQ-5D is the preferred measure of

health-related quality of life in adults and concluded that the utility data available from the EQ-5D was the most appropriate for its decision making. The Committee noted that the results from the EQ-5D analyses (see section 3.11) suggested that nalmefene plus BRENDA improved a person's health-related quality of life compared with placebo plus BRENDA. The Committee was also aware that it had heard from the patient experts that health-related quality of life was important and any treatment that could have a positive impact on quality of life was considered valuable (see section 4.1). The Committee agreed that the EQ-5D data showed that nalmefene plus BRENDA improved health-related quality of life compared with placebo plus BRENDA.

Cost effectiveness

4.9 The Committee considered the company's economic model and the review and exploratory sensitivity analyses performed by the ERG. It discussed the company's general approach to developing the nalmefene plus psychosocial support economic model. It noted that the ERG considered the company's model to be well structured with most of the assumptions being unfavourable to nalmefene. The ERG commented that the company had not included a half-cycle correction and that this was a limitation of the model. However, the ERG acknowledged that the impact of a half-cycle correction in the monthly time cycles was likely to be small. The Committee concluded that the outlined structure of the model adhered to the NICE reference case for economic analysis and was accepted for assessing the cost effectiveness of nalmefene plus psychosocial intervention.

4.10 The Committee considered the company's cost-effectiveness analyses for comparing nalmefene plus psychosocial support with psychosocial support alone. It noted that the company had provided a base-case analysis in which the psychosocial support in both the intervention and comparator groups was BRENDA, which was an intervention of lower intensity than that recommended in NICE clinical guideline 115 (see

section 3.28). The Committee accepted the company's base-case incremental cost-effectiveness ratio (ICER) that nalmefene plus psychosocial support dominated psychosocial support alone. The Committee was aware of the ERG's comments that the evaluation carried out in the model does not meet the final scope issued by NICE because the scope stated psychosocial intervention as defined by NICE clinical guideline 115. The Committee noted that the ERG had formulated 4 comparisons testing the robustness of the cost effectiveness of nalmefene plus psychosocial intervention relevant to the decision problem defined in the scope, that is, psychosocial intervention as defined in NICE clinical guideline 115 (see section 3.37). The Committee discussed which of the ERG's 4 comparisons were most appropriate for its decision-making. The Committee was aware of its decision to accept that brief or extended brief interventions as the appropriate comparator for nalmefene and that it was satisfied that the psychosocial support used in the nalmefene studies (BRENDA, as part of the intervention and the comparator) closely represented current clinical practice in England. The Committee therefore agreed that the ERG's comparison 1 (which corresponded with the company's base-case analysis) was the most appropriate analysis.

4.11 The Committee considered the ERG's exploratory amendments in comparison 1. It noted the amendments made by the ERG to the company's base case (see sections 3.38 and 3.39). The Committee noted that the changes did not include amending the company's assumption that people would remain on treatment (regardless of drinking risk level) for the full year. It discussed whether the company's assumption that patients would remain on treatment for 12 months regardless of drinking level and response was reasonable. The Committee heard from both the clinical experts and the ERG that it is unlikely that GPs would allow a patient to continue treatment and continue drinking at a high drinking risk level for up to 1 year. 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. The Committee was aware that it was unclear to the ERG if such changes to the duration of treatment would be favourable or unfavourable to nalmefene plus psychosocial support. The ERG had commented that it was highly unlikely to change the cost-effectiveness results from comparison 1. The Committee considered the 7 exploratory analyses carried out by the ERG and the ERG's exploratory base case, which combined 4 of the ERG'S exploratory analyses: medium-risk drinkers relapsed to high or very high risk, all of the patients who withdrew for nalmefene-related responses also withdrew from psychosocial support, the average cost of medically assisted withdrawal was £645 per patient and that the cost of expert prescribing was £119. With these assumptions taken into account, the ERG's exploratory base case indicated that nalmefene plus psychosocial support still dominated psychosocial support alone (that is, was less expensive and more effective). The Committee also discussed that when the ERG presumed no second-line treatments were available, the incremental cost-effectiveness ratio (ICER) increased to £5100 cost per quality-adjusted life year (QALY) gained for nalmefene plus psychosocial support compared with psychosocial support alone. It concluded that based on the analyses provided by the ERG the ICER would lie somewhere between nalmefene plus psychosocial support being dominant and £5100 per QALY gained compared with psychosocial support alone.

4.12 The Committee also discussed whether any other factors should be taken into account when considering the cost effectiveness of nalmefene plus psychosocial support. It noted that adopting a wider perspective than the NHS and personal social services, as included in the remit from the Department of Health, resulted in nalmefene plus psychosocial support still dominating psychosocial support alone. The 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 Committee was aware that it had heard from patient experts that reducing alcohol consumption was of considerable

importance to family members and carers (see section 4.1). The Committee agreed that the utility values used in the economic model may have underestimated the true benefit of nalmefene plus psychosocial support. Although aware of the uncertainty about whether the results from the 3 nalmefene clinical studies are generalisable to patients seen in practice in England (see section 4.4) and the uncertainty associated with the post hoc subgroup analyses (see section 4.6), taking into account the wider societal perspective and the possible underestimation of the utility values, the Committee agreed that the most plausible ICER was likely to be lower than £5100 per QALY gained. The Committee therefore concluded that nalmefene given in conjunction with psychosocial support was a cost-effective use of NHS resources compared with psychosocial support alone for treating people with alcohol dependence who have a high drinking risk level, without physical withdrawal symptoms and who do not require immediate detoxification.

4.13 The Committee discussed the issue of adherence to nalmefene treatment in clinical practice, given that it should only be prescribed in conjunction with psychosocial support focusing on treatment adherence and reducing alcohol consumption. The Committee was aware that the summary of product characteristics for nalmefene indicates that physicians should continue to assess the patient's progress in reducing alcohol consumption and treatment adherence and that physicians must take this into consideration when prescribing nalmefene plus psychosocial support. The clinical experts commented 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 intervention sessions, there are many who would be sufficiently motivated to adhere to all aspects of the treatment. The Committee heard from the clinical experts that patients taking nalmefene would usually be given information to ensure that they understand why adherence to treatment (in terms of when they take their medication, recording of alcohol consumption and attendance at psychosocial support sessions) is

important. The Committee concluded that treatment adherence for both nalmefene and psychosocial support is an important consideration for physicians when prescribing treatment.

4.14 The Committee noted the concerns raised during both its meetings and the consultation regarding difficulties that may be encountered complying with the implementation period in which to provide funding for nalmefene. It was aware of the requirement for the relevant health bodies (clinical commissioning groups, NHS England and local authorities) to provide funding to ensure the technology is available within 3 months, from the date the recommendation is published by NICE. The Committee noted that the provision of psychosocial intervention differs throughout England, and the licence for nalmefene mandates that treatment should be given in combination with psychosocial support. The Committee highlighted that it would be reasonable for NICE to reflect on whether the standard 3 month implementation period is appropriate.

4.15 The Committee noted the potential equality issue raised by a patient expert and a Committee member in the meeting that families may be stigmatised for having a family member with alcohol dependence. It also noted the equality issue raised in a clinical expert statement, suggesting that there could be issues with consent of treatment in certain populations in terms of cognitive decline and learning disability. The Committee considered that healthcare professionals should be mindful of the need to ensure equality of access to treatment for patients with disabilities. 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.

Summary of Appraisal Committee's key conclusions

TAXXX	Appraisal title: Nalmefene for reducing alcohol consumption in people with alcohol dependence	Section
Key conclusions		
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 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, and • who do not require immediate detoxification. 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 level 2 weeks after initial assessment.		1.1
The Committee understood 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.The Committee concluded that psychosocial intervention in the form of brief or extended brief intervention is a valid comparator for		4.2

nalmefene plus psychosocial support and the most appropriate comparator for this appraisal.	
The Committee noted the uncertainty and conflicting opinions among the stakeholders regarding the most appropriate setting for prescribing nalmefene plus psychosocial intervention. However the Committee was aware that making specific recommendations about the setting for prescribing nalmefene was outside the scope of a technology appraisal.	4.3
The Committee was aware that the psychosocial support provided in the studies was in the form of BRENDA. It heard from experts that although BRENDA is not used in its entirety in clinical practice, most the components within it are currently provided in the form of brief or extended brief interventions, and could be administered by health professionals. The Committee accepted that BRENDA closely resembled current established practice and the clinical effectiveness evidence based on the comparison with BRENDA was relevant to clinical practice.	4.5
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 for these analyses.	4.6
The Committee agreed that the most plausible incremental cost effectiveness ratio (ICER) was likely to be lower than £5100 per quality adjusted life year (QALY) gained, and therefore concluded that nalmefene plus psychosocial support was a cost-effective use of NHS resources compared with psychosocial support alone.	4.12
Current practice	

Clinical need of patients, including the availability of alternative treatments	The Committee heard from patient experts that alcohol dependency can have a substantial negative effect on quality of life, including physical, mental and financial constraints for the patient and their family.	4.1
The technology		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The Committee heard from the clinical experts that nalmefene plus psychosocial support is an important addition to the treatment pathway as it is the first pharmacological intervention that is specifically for alcohol reduction rather than abstinence.	4.2
What is the position of the treatment in the pathway of care for the condition?	The Committee heard from the clinical experts that nalmefene plus psychosocial support is an important addition to the treatment pathway as it is the first pharmacological intervention that is specifically for alcohol reduction rather than abstinence.	4.2
Adverse reactions	The summary of product characteristics lists the following adverse reactions for nalmefene: nausea, dizziness, insomnia and headaches. For full details of adverse reactions and contraindications, see the summary of product characteristics.	2.3
Evidence for clinical effectiveness		

Availability, nature and quality of evidence	There were 3 randomised controlled trials (ESENSE1, ESENSE2 and SENSE) in adults with alcohol dependence, comparing 18 mg nalmefene (on an as-needed basis) plus psychosocial support with placebo plus psychosocial support. Psychosocial support provided in the studies was in the form of BRENDA. The Committee noted that there were no trials directly comparing nalmefene plus psychosocial support with naltrexone plus psychosocial intervention, and the company had not presented an indirect comparison of the 2 treatments.	4.4, 4.5 4.7

Relevance to general clinical practice in the NHS	The Committee heard from clinical experts that that psychosocial intervention (brief or extended brief intervention) provided in the primary care setting, was first-line treatment in England for people with alcohol dependency who have a high or very high drinking risk level without physical withdrawal symptoms and who do not require immediate detoxification.	4.2
	The Committee was aware that Alcohol-use disorders (NICE clinical guideline 115) recommends that psychosocial intervention should typically consist of weekly sessions of 60 minute duration over a 12 week period but the current services available in England have difficulty providing this level of treatment.	4.3
	The Committee was also aware that NICE clinical guideline 115 recommends that pharmacological interventions (such as naltrexone) are considered for people with mild alcohol dependence, only in those for whom psychosocial intervention alone has not helped or if people have specifically requested it. The clinical expert explained 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.	4.2

Uncertainties generated by the evidence	The Committee noted that the 2 ESENSE studies excluded people with severe psychiatric conditions and patients with severe medical comorbidities but took on board the company's consultation response detailing that at the UK sites in the SENSE trial, nalmefene was provided to patients with stable psychiatric co-morbidity and who were taking multiple medications. It also noted that none of the sites in the ESENSE trials were in the UK and only 5 sites in the SENSE trial were UK based. The Committee concluded that the baseline characteristics of the populations in the 3 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 plus psychosocial support.	4.4
	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 for these analyses.	4.6
	The Committee was aware that it had heard from the clinical experts that naltrexone plus psychosocial intervention was not part of	4.7

4.7

	established practice for the reduction of alcohol consumption and agreed that naltrexone plus psychosocial intervention was not 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.	
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The Committee considered that it should only consider the post hoc subgroup analyses in the marketing authorisation. No further subgroups were considered by the Committee.	4.6
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The Committee noted that the results from the post hoc subgroup analyses suggested that people in the nalmefene plus BRENDA group had fewer heavy drinking days per month and total alcohol consumption per day compared with those who received placebo plus BRENDA.	4.6
Evidence for cost effectiveness		

Availability and nature of evidence	Having heard from the clinical experts that naltrexone plus psychosocial intervention was not part of established practice for the reduction of alcohol consumption, 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.	4.7
	The ERG considered the company's model to be well structured with most of the assumptions being unfavourable to nalmefene but commented that the company had not included a half-cycle correction and that this was a limitation of the model.	4.9
	The Committee concluded that the outlined structure of the model adhered to the NICE reference case for economic analysis and was accepted for assessing the cost effectiveness of nalmefene plus psychosocial support.	4.9

Uncertainties around and plausibility of assumptions and inputs in the economic model	The Committee discussed whether the company's assumption that patients would remain on treatment for 12 months regardless of drinking level and response was reasonable. Both the clinical experts and the ERG suggested it unlikely that GPs would allow a patient to continue treatment and continue drinking at a high drinking risk level for up to 1 year. The Committee was aware that it was unclear to the ERG if such changes to the duration of treatment would be favourable or unfavourable to nalmefene plus psychosocial support.	4.11
Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	The 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 Committee agreed that the utility values used in the economic model may have underestimated the true benefit of nalmefene plus psychosocial support because it did not take into account health-related quality of life of family and carers.	4.12

Are there specific groups of people for whom the technology is particularly cost effective?	Not applicable to this appraisal.	-
What are the key drivers of cost effectiveness?	The Committee considered the ERG's exploratory amendments in comparison 1 and noted that the length of time for which people were treated with nalmefene was unlikely to affect the ICER. The Committee considered the 7 exploratory analyses carried out by the ERG and the ERG's exploratory base case, which combined 4 of the ERG'S exploratory analyses: medium-risk drinkers relapsed to high or very high risk, all of the patients who withdrew for nalmefene-related responses also withdrew from psychosocial support, the average cost of medically assisted withdrawal was £645 per patient and that the cost of expert prescribing was £119 and concluded the ICER was unlikely to be affected.	4.11

Most likely cost-effectiveness estimate (given as an ICER)	The Committee agreed that the most plausible ICER was likely to be lower than £5100 per QALY gained. The Committee therefore concluded that nalmefene plus psychosocial support was a cost-effective use of NHS resources compared with psychosocial support alone for treating people with alcohol dependence who have a high drinking risk level, without physical withdrawal symptoms and who do not require immediate detoxification.	4.12
Additional factors taken into account		
Patient access schemes (PPRS)	Not applicable to this appraisal.	-
End-of-life considerations	Not applicable to this appraisal.	-
Equalities considerations and social value judgements	The Committee considered that healthcare professionals should be mindful of the need to ensure equality of access to treatment for patients with disabilities (in terms of issues with consent of treatment in certain populations, for example cognitive decline and learning disability). 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.	4.15

5 Implementation

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.

5.2 When NICE recommends a treatment 'as an option', the relevant health bodies (clinical commissioning groups, NHS England and local authorities) must make sure it is available within the period set out in the paragraph above. This means that, if a patient has alcohol dependence and the doctor responsible for their care thinks that nalmefene is the right treatment, it should be available for use, in line with NICE's recommendations.

5.3 NICE has developed tools [link to www.nice.org.uk/guidance/TAXXX] to help organisations put this guidance into practice (listed below). [NICE to amend list as needed at time of publication]

- Slides highlighting key messages for local discussion.
- Costing template and report to estimate the national and local savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

6 Related NICE guidance

Details are correct at the time the final appraisal determination goes out for appeal and will be removed when the final guidance is published. Further information is available on the NICE website.

Published

- Psychosis with coexisting substance misuse. NICE clinical guideline 120 (2011).
- Alcohol dependence and harmful alcohol use. NICE clinical guideline 115 (2011).
- Alcohol-use disorders: physical complications. NICE clinical guideline 100 (2010).
- Alcohol-use disorders: preventing harmful drinking. NICE public health guidance 24 (2010).
- School-based interventions on alcohol. NICE public health guidance 7 (2007).
- Interventions to reduce substance misuse among vulnerable young people. NICE public health guidance 4 (2007).

NICE Pathways

- Alcohol-use disorders. NICE pathway (2013).

Review of guidance

6.1 The guidance on this technology will be considered for review 3 years after publication of the guidance. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Professor Gary McVeigh
Chair, Appraisal Committee
September 2014

7 Appraisal Committee members, guideline representatives and NICE project team

Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3 year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Professor Gary McVeigh (Chair)
Professor of Cardiovascular Medicine, Queens University Belfast and Consultant Physician, Belfast City Hospital

Dr Lindsay Smith (Vice Chair)
General Practitioner, West Coker Surgery, Somerset

Dr Andrew Black
General Practitioner, Mortimer Medical Practice, Herefordshire

Professor David Bowen
Consultant Haematologist, Leeds Teaching Hospitals NHS Trust

Dr Matthew Bradley
Therapy Area Leader, Value Evidence & Outcomes (Global), GlaxoSmithKline

Miss Tracey Cole

Lay Member

Professor Peter Crome

Honorary Professor, Department of Primary Care and Population Health, UCL

Professor Simon Dixon

Professor of Health Economics, University of Sheffield

Mrs Susan Dutton

Senior Medical Statistician, Oxford Clinical Trials Research Unit

Dr Alexander Dyker

Consultant Physician, Wolfson Unit of Clinical Pharmacology, University of Newcastle

Mr Christopher Earl

Surgical Care Practitioner, Wessex Neurological Centre at Southampton University Hospital

Mrs Gillian Ells

Prescribing Advisor – Commissioning, NHS Hastings and Rother and NHS East Sussex Downs and Weald

Professor Paula Ghaneh

Professor and Honorary Consultant Surgeon, University of Liverpool

Professor Carol Haigh

Professor in Nursing, Manchester Metropolitan University

Dr Alan Haycox

Reader in Health Economics, University of Liverpool

Professor John Henderson

Professor of Paediatric Respiratory Medicine, University of Bristol and Bristol Royal Hospital for Children

Dr Paul Hepple

General Practitioner, Muirhouse Medical Group

Professor Steven Julious

Professor of Medical Statistics, University of Sheffield

Dr Tim Kinnaird

Lead Interventional Cardiologist, University Hospital of Wales, Cardiff

Ms Emily Lam

Lay member

Dr Paul Miller

Director, Payer Evidence, AstraZeneca

Dr Malcolm Oswald

Lay member

Professor Femi Oyebode

Professor of Psychiatry & Consultant Psychiatrist, The National Centre for Mental Health

Dr John Radford

Director of Public Health, Rotherham Primary Care Trust and MBC

Dr Murray Smith

Associate Professor in Social Research in Medicines and Health, University of Nottingham

Ms Pamela Rees

Lay member

Mr Cliff Snelling

Lay member

Professor Carolyn Young

Consultant neurologist, Walton Centre for Neurology & Neurosurgery

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Dr Caroline Hall
Technical Lead

Dr Nicola Hay
Technical Adviser

Nwamaka Umeweni
Technical Adviser

Donna Barnes
Project Manager

8 Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by the School of Health and Related Research (ScHARR):

- Stevenson M, Pandor A, Stevens J, Rawdin A, Wong R, Morgan MY, Rice P, Thompson J. Nalmefene for reducing alcohol consumption in people with alcohol dependence: A Single Technology Appraisal. School of Health and Related Research (ScHARR), 2014.

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to give their expert views. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I. Company/sponsor:

- Lundbeck

II. Professional/expert and patient/carer groups:

- ADFAM
- Alcohol Concern
- British Liver Trust
- Lifeline Project
- British Association for Psychopharmacology
- National Substance Misuse Non-Medical Prescribing Forum
- Royal College of General Practitioners
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians
- Royal College of Psychiatrists

III. Other consultees:

- Department of Health
- NHS England
- NHS Stafford and Surrounds CCG
- NHS Warrington CCG
- Welsh Government

IV. Commentator organisations (did not provide written evidence and without the right of appeal):

- Association of Directors of Public Health
- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- Medicines and Healthcare products Regulatory Agency
- Social Care Institute for Excellence
- Bristol-Myers Squibb Pharmaceuticals
- Institute of Alcohol Study

- School of Health and Related Research (ScHARR)
- National Institute for Health Research Health Technology Assessment Programme

C. The following individuals were selected from clinical expert and patient expert nominations from the consultees and commentators. They gave their expert personal view on nalmefene by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr Chris Daly, Lead Consultant Addiction Psychiatrist, nominated by the Royal College of Psychiatrists – clinical expert
- Simon Greasley, Specialist Nurse Practitioner, nominated by the Royal College of Nursing – clinical expert
- Andrew Langford, nominated by British Liver Trust – patient expert
- Oliver Standing, nominated by ADFAM– patient expert

E. Representatives from the following company/sponsor attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Lundbeck