NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Nalmefene for reducing alcohol consumption in people with alcohol dependence

This premeeting briefing is a summary of:

- the evidence and views submitted by the manufacturer, the consultees and their nominated clinical specialists and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document is a summary of the information available after the manufacturer has checked the ERG report for factual inaccuracies.

Key issues for consideration

Clinical-effectiveness

- What is the likely sequence of treatment for high and very high drink risk patients? The ERG disagree with the manufacturer that nalmefene would only be used as a first-line treatment. Will people be treated with nalmefene after not responding to PI alone?
- The ERG raised concerns about the generalisability of the population in the 3 nalmefene trials to clinical practice in England
  - The 3 trials for nalmefene excluded people based on co-morbities; ESENSE 1 and 2 trials excluded patients with co-morbid psychiatric conditions and SENSE excluded patients with severe psychiatric conditions. In addition, people were also excluded from the nalmefene trials if they were taking certain concomitant medication such as drugs for angina, anticoagulants, anticonvulsants, insulin, sedatives and systemic steroids. The manufacturer suggested that many people who are alcohol dependent have diagnosed medical conditions and/or psychiatric conditions.

  - The ERG highlighted that only a small minority of people within the 3 nalmefene trials were from the UK (SENSE trial only, 5 sites out of a total of 60) and no data were provided in the manufacturer's submission on the variability of the outcomes between recruiting European countries.

Are the populations in the 3 nalmefene trials generalisable to clinical practice in England?

- The ERG raised concerns about the generalisability of BRENDA (the psychosocial intervention [PI] used in the 3 nalmefene trials) to clinical practice in England and/or to the recommendations in Alcohol-use disorders (NICE clinical guideline [CG] 115). The manufacturer assumed that BRENDA is comparable with the PI support provided in England. BRENDA was delivered at weekly intervals for the first 2 weeks and monthly thereafter (sessions were limited to approximately 15 to 30 minutes except for the first session which was administered at randomisation and lasted approximately 30 to 40 minutes). The manufacturer assumed that PI treatment would mostly be provided by general practitioners. The ERG commented that its clinical advisors disagreed with this assumption, as they had stated that in best practice a greater proportion would be treated in specialist centres. The ERG also stated that this is in stark contrast to the recommendations in NICE CG115, which recommends that PI (including behavioural therapies, cognitive behavioural therapy and behavioural couples therapies) should consist typically of weekly sessions of 1 hour's duration over a 12-week period and be delivered typically by a clinical psychologist. Is BRENDA generalisable to clinical practice in England and/or to the recommendations in NICE CG115?
- Post-hoc subgroup analysis was carried out on people in the nalmefene trials (ESENSE 1, 2 and SENSE trials) and these were subsequently the licensed population. The ERG commented that the robustness of the safety and efficacy of nalmefene could be unknown although it acknowledged that the European Medicines Agency's (EMA) recognised the validity of this analysis. Is this analysis sufficiently robust to make a decision on the clinical-effectiveness of nalmefene?
- The manufacturer stated that it could not include naltrexone as a comparator even though it was included in the decision problem because there was insufficient data

available for comparison with nalmefene. An indirect comparison was also rejected by the manufacturer because the set-up of the trials and outcomes measure were too different. Should the manufacturer have undertaken an indirect comparison, albeit an imperfect one? Is there sufficient evidence on which to base a decision?

Cost-effectiveness

- The manufacturer's model did not incorporate a half-cycle correction. The ERG acknowledged that the impact of half-cycle correction in the monthly time cycles is likely to be small. The ERG believed that omitting half-cycle correction is a limitation of the manufacturer's economic model. A more accurate estimation of cost-effectiveness would be obtained by assuming that all events took place midway through the year (for years 2 to 5) rather than all occurring at the start of the year. Should the manufacturer have included a half-cycle correction?
- The manufacturer assumed in the model that patients would stay on current treatment for 12 months before changing to an alternative if they had not responded, regardless of the drinking risk. The clinical advisors to the ERG regarded 12 months as too long and instead thought patients would change treatment or receive more intensive treatment after 3 months. Is the manufacturer's assumption appropriate?
- The ERG stated that the largest limitation of the manufacturer's cost-effectiveness analysis was that no formal comparison was performed between nalmefene plus PI and PI alone, where PI was that included in the NICE CG115. The ERG noted that 4 comparisons can be formulated and the ability to provide robust estimates of cost-effectiveness of nalmefene in addition to PI decreases as the comparisons become more relevant to the decision problem:
  - Comparison 1: A comparison of nalmefene plus PI being compared with PI, with PI being approximated by BRENDA as used in the 3 nalmefene trials. The ERG stated that this would not meet the decision problem specified in the final scope issued by NICE as BRENDA is not equivalent to PI as recommended in NICE CG115. The ERG believed the manufacturer's base-case had estimated a plausible cost-effectiveness estimate for this comparison. The cost

effectiveness analysis suggested that nalmefene plus PI dominated PI. Given the differences between BRENDA and the PIs in NICE CG115, is it appropriate to use the results from this comparison as a basis for decision making?

- Comparison 2: A comparison of nalmefene plus PI being compared with PI alone with PI being that recommended in NICE CG115. The ERG stated that the threshold analysis as performed by the manufacturer (Scenario 7 analysis), using the greater additional costs of such PI would provide some information on this comparison. Scenario 7 indicated that the efficacy difference between nalmefene and PI and PI alone would need to be reduced by 70.3% for nalmefene and PI to have a cost per QALY of £20,000 and to be reduced by 77.2% for nalmefene in addition to PI to have a cost per QALY of £30,000. The ERG's exploratory analyses produced similar results to those produced by the manufacturer. The clinical advisors to the ERG did not feel confident in expressing an opinion on whether the actual reduction would be greater or lower than a 60-70% threshold. Does this analysis adequately capture the uncertainty around the relative effectiveness of nalmefene plus PI compared with PI alone, with PI being that recommended in NICE CG115? Is it appropriate to use the results from this comparison as a basis for decision making?
- Comparison 3: A comparison of delayed addition of nalmefene use for those who did not respond to PI alone, with immediate use of nalmefene plus PI; in both cases PI is that recommended in NICE CG115. The manufacturer did not estimate an ICER for this comparison. The ERG stated that there are very few appropriate data to assess nalmefene within this comparison. The ERG stated that it is probable that delayed use of nalmefene in people who do not respond to PI as recommended by NICE CG115 was more cost-effective than immediate use of nalmefene in all patients. Is it appropriate to use the results from this comparison as a basis for decision making?
- Comparison 4: A comparison of the delayed addition of nalmefene for those who did not respond to PI or immediate use of nalmefene plus PI compared with the delayed addition of naltrexone in those who do not respond to PI; in all cases PI is that recommended in NICE CG115. The ERG stated that there

were very few appropriate data to assess nalmefene within this comparison. As such the ERG did not feel comfortable in providing an estimate of the ICER for this comparison. Is there sufficient evidence to demonstrate that nalmefene in addition to PI is cost-effective in this comparison?

1 Background: clinical need and practice

1.1 Alcohol dependence is characterised by craving, tolerance and a preoccupation with alcohol. It is defined as a maladaptive pattern of alcohol use, leading to clinically significant impairment or distress. Severity may be defined using measures of symptoms and behaviours and/or amount of alcohol consumed. The Alcohol Use Disorders Identification Test is an initial screen for alcohol related issues, and the Severity of Alcohol Dependence Questionnaire measures alcohol related symptoms, behaviours and consumption (mild, moderate or severe alcohol dependence). The World Health Organisation categorise alcohol consumption in different health risk levels. High drinking risk level is ≥ 60 g/day of pure alcohol for men and ≥ 40 g/day for women.

1.2 In England, alcohol dependence affects approximately 4% of people aged 16-65 years (6% of men and 2% of women), about 1.1 million people, of whom 6% seek treatment. It is estimated that around 85,000 people with moderate or severe dependence receive specialist treatment each year. Alcohol dependence is associated with an increased rate of significant mental and physical disorders, including cardiovascular disease, neurological disorders (for example seizures and delirium tremens), gastrointestinal disorders (for example liver disease and acute and/or chronic pancreatitis), mental health disorders (for example depression and anxiety disorders) and Wernicke's encephalopathy.

1.3 In 2012 there were 8367 alcohol-related deaths in the UK, 381 fewer than in 2011. Males accounted for 65% of all alcohol-related deaths and were highest among men aged 60 to 64 years (42.6 deaths per 100,000

population) and in women aged 55 to 59 years (22.2 deaths per 100,000). Heavy drinking can reduce life expectancy by 10-12 years.

1.4 For people with mild alcohol dependence, NICE CG115 states that assisted withdrawal programmes are usually not needed and recommends offering a PI (such as cognitive behavioural therapies, behavioural therapies, behavioural couples therapy or social network and environment-based therapies) focused specifically on alcohol-related cognitions, behaviour, problems and social networks. For people with moderate alcohol dependence, assisted withdrawal programmes are usually needed but can be managed in a community setting and for people with severe alcohol dependence assisted withdrawal programmes are needed usually in an inpatient or residential setting. NICE CG115 also recommends specific pharmacological treatments for assisted withdrawal from alcohol and for the prevention of relapse after assisted withdrawal.

2 The technology

2.1 Nalmefene (Selincro, Lundbeck) is an opioid receptor modulator, which exhibits antagonist activity at μ and δ opioid receptors, and partial agonist at κ opioid receptors. It is administered orally. Nalmefene has a UK marketing authorisation for ‘the reduction of alcohol consumption in adult patients with alcohol dependence who have a high drinking risk level (DRL) without physical withdrawal symptoms and who do not require immediate detoxification’.

2.2 Nalmefene is available in an 18 mg film coated tablet, with a maximum dose of 1 tablet per day. Nalmefene should only be prescribed in conjunction with continuous psychosocial support focused on treatment adherence and reducing alcohol consumption. The drug should only be initiated 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 priced at £42.42 for a pack of 14 tablets or £84.84 for a packet of 28 tablets (excluding VAT; 'British national formulary' [BNF] (online April 2014). Costs may vary in different settings because of negotiated procurement discounts

3 Remit and decision problem(s)

3.1 The remit from the Department of Health for this appraisal was: To appraise the clinical- and cost-effectiveness (allowing adoption of a wider perspective than the NHS and Personal and Social Services) of nalmefene within its licensed indication for reducing alcohol consumption in people with alcohol dependence.

	Final scope issued by NICE	**Decision problem addressed in the submission**
Population	Adults with mild alcohol dependence (as defined in NICE CG115) who have a high DRL (≥ 60 g/day of pure alcohol for men and ≥ 40 g/day for women) without physical withdrawal symptoms and who do not require immediate detoxification	Adults with mild alcohol dependence who have a high DRL without physical withdrawal symptoms, do not require immediate detoxification, and continue to have a high DRL 2 weeks after initial assessment
Intervention	Nalmefene in conjunction with psychosocial support (as defined in NICE Clinical Guidelines 115)	Nalmefene plus psychosocial intervention

Comparators	(i) Psychological intervention such as cognitive behavioural therapies, behavioural therapies or social network and environment-based therapies alone (as defined in NICE Clinical Guideline 115). (ii) Naltrexone (in conjunction with psychosocial support as defined in NICE Clinical Guideline 115)	Psychosocial intervention such as cognitive behavioural therapies, behavioural therapies, or social network and environment-based therapies

In the nalmefene trials PI, in the form of BRENDA, was employed. BRENDA was delivered at weekly intervals for the first 2 weeks and monthly thereafter, which the ERG commented does not fit with the recommendations for PI within NICE CG115. The ERG suggested it was not clear how the results from the nalmefene trials would apply to people who received different forms or frequencies of PI.

	Final scope issued by NICE	Decision problem addressed in the submission
Outcomes	The outcome measures to be considered include: • alcohol consumption • alcohol dependence symptoms • compliance/concordance with treatment • objective measures of alcohol consumption • hospitalisations • controlled drinking • change in number of heavy drinking days • morbidity • mortality • adverse effects of treatment • health-related quality of life.	Outcomes measures considered in the submission include: • alcohol consumption • alcohol dependence symptoms • proportion of responders • adherence to medication • liver function and other clinical safety laboratory tests (GGT, ALAT, MCV, %CDT) • change in number of HDDs • adverse effects of treatment • health-related quality of life.

Economic evaluation	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs in the reference case will be considered from an NHS and Personal Social Services perspective. If evidence allows sensitivity analyses should be presented taking into account the wider impacts of alcohol dependence, specifically including: • Social and crime issues, including impacts on domestic violence and prisons; • Social effects of alcohol dependence of adults on children; and • The effects of driving while under the influence of alcohol.	The submission will be in line with the final scope. A cost-effectiveness assessment aligned with the reference case presenting cost/QALYs is included. The model also provides outcomes in terms of alcohol-attributable hospitalisations, criminal justice encounters, and mortality.

3.2 The technology is being positioned by the manufacturer as first-line treatment for people with high or very high risk drinking levels.

4 Clinical-effectiveness evidence

4.1 The manufacturer conducted 2 systematic reviews, 1 evaluating the pharmacological agents nalmefene and naltrexone for the reduction of alcohol consumption and the second to identify trials for psychosocial intervention (PI) used in alcohol dependence.

Nalmefene compared with psychological intervention

4.2 The manufacturer identified and included 3 studies that investigated the effect of nalmefene plus PI compared with placebo plus PI. These trials were ESENSE 1, ESENSE 2 and SENSE.

4.3 The ESENSE 1 (n=604; nalmefene plus PI and placebo plus PI) and ESENSE 2 (n=718; nalmefene plus PI and placebo plus PI) trials were identical in design, being randomised, double-blind, multinational, multicentre, parallel-group, placebo-controlled trials to determine the efficacy of as needed oral 18mg nalmefene plus PI (in the form of BRENDA) compared with placebo plus PI, in adults with alcohol dependence over a 6 month period.

4.4 BRENDA provided PI treatment based on 6 components. The first part was a biopsychosocial evaluation followed by a report of findings from the evaluation provided to the patient. The next stage involved empathy for the patient and assessing their needs, providing direct advice, assessing patient reaction to advice and adjusting the treatment plan as required. All sessions were provided by trained professionals and were delivered at weekly intervals for the first 2 weeks and then monthly. Sessions were all 15-30 minutes except for the first session which was 30-40 minutes.

4.5 The participants in both ESENSE 1 and 2 were diagnosed with a Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) diagnosis of dependence and had at least 6 heavy drinking days (HDDs) in the preceding 28 days. A HDD was defined as ≥60 g/day [≥7.5 units] for men and ≥40 g/day [≥5 units] for women. In addition, people had an average daily alcohol consumption level conferring medium risk or higher (defined as ≥40g/day [≥5 units/day] for men and ≥20g/day [2.5 units/day] for women) or ≤ 14 abstinent days in the 4 weeks preceding the screening visit. In both studies, individuals with severe medical conditions or psychiatric comorbidities were excluded.

4.6 Both ESENSE studies contained 4 periods. The first was a 1-2 week screening period after which participants were randomised 1:1 to either the nalmefene or placebo group for 24 weeks. Next participants were instructed to take 1 tablet (the maximum dose per day) 1-2 hours before a risk of heavy drinking. If the participants started to drink without taking a tablet they were advised to take one as soon as possible. The participants who completed the 6 month trial entered a 4 week, double-blind, run-out period to evaluate any treatment discontinuations effects. The participants initially randomised to nalmefene were re-randomised 1:1 to receive nalmefene or placebo and the participants in the original 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.

4.7 The primary outcomes for the ESENSE studies were changes from baseline in the monthly number of HDDs and total alcohol consumption (TAC) in month 6 (in line with the EMA's guideline on the development of medicinal products for the treatment of alcohol dependence, 2010). Participants self-reported their daily alcohol consumption using the timeline follow-back method to estimate retrospectively how many standard drinks they had consumed each day (over a 24 hour period from 6am to 6am). Secondary outcomes included effect of nalmefene on; proportion of responders based on different drinking measures, alcohol dependence symptoms and clinical status, liver function and other clinical safety laboratory tests, pharmacoeconomic outcomes, treatment withdrawal effects after 24 weeks, safety and tolerability of nalmefene, and quality of life measures (SF-36 and EQ-5D).

4.8 The SENSE (n=675) trial was a randomised, double-blind, multinational, multicentre, parallel-group, placebo-controlled trial designed to collect long-term safety data on, as needed oral 18mg nalmefene plus PI (BRENDA) compared with placebo plus PI, in adults over a 12 month period. The people were diagnosed as being alcohol dependent using the DSM-IV-TR diagnosis. The study was primarily designed to collect long-

term safety data on nalmefene. After study initiation the protocol was amendment to include efficacy analyses at 6 months. Of the trial population 62% of people completed the 12 month study.

4.9 The primary outcome for the SENSE study was again change from baseline in monthly total alcohol consumption and HDDs at month 6. Secondary outcomes including all those measured in the ESENSE trials (except for withdrawal after 24 weeks) but also long-term effect on reduction of alcohol consumption, alcohol dependence symptoms and clinical status, liver function and other biological laboratory tests.

4.10 In ESENSE 1 and 2, approximately 78% of participants had a high/very high DRL at baseline. In the first 2 weeks of screening a large number of people reduced their alcohol intake to less than 6 HDDs per month or to below a medium DRL (18% in ESENSE 1 and 33% in ESENSE 2) and therefore no longer within the inclusion criteria. In the SENSE trial 52% of participants enrolled had a high/very high DRL at baseline. Following agreement of the Scientific Advisory Group (SAG) to the EMA, the manufacturer performed a post-hoc subgroup analysis on the subgroup of patients in ESENSE 1, ESENSE 2 and SENSE with a high/very high DRL at baseline who maintained a high/very high DRL at randomisation. The manufacturer stated that the purpose of these analyses were to define the patient population who were expected to benefit most from nalmefene. The manufacturer highlighted that the SAG recognised the validity of the subgroup analyses and that these analyses form the basis of the licensed population in the marketing authorisation for nalmefene.

4.11 All analyses were conducted according to the modified intention to treat principle using a mixed model repeated measures approach. In response to a clarification request by the ERG and NICE, the manufacturer commented that the mixed model repeated measures analysis used all available data measured over each month during the treatment period and

provides an unbiased estimate of the treatment effect under the assumption that missing data are missing at random.

4.12 The results for the primary outcome measure in ESENSE 1, ESENSE 2 and SENSE in the licensed population (participants with a high/very high DRL at baseline and radomisation) are shown in tables 1 and 2 below.

Table 1. Mean difference to placebo in the change from baseline to month 6 in HDDs and TAC in the licensed population of the ESENSE1 and ESENSE2 trials (adapted from table B11, p93 of the manufacturer's submission)

Trial	Number of participants at baseline		Mean difference to placebo in the change from baseline to month 6	95% CI	*P* value
	Nalmefene + PI	Placebo + PI			
ESENSE1	171	167	−3.7 HDDs/month	−5.9 to −1.5	0.001
			−18.3 g/day (TAC)	−26.9 to −9.7	< 0.001
ESENSE2	148	155	−2.7 HDDs/month	−5.0 to −0.3	0.025
			−10.3 g/day (TAC)	−20.2 to −0.5	0.040
CI = confidence interval; DRL = drinking risk level; HDD = heavy drinking day; PI = psychosocial intervention; TAC = total alcohol consumption					

Table 2. Mean difference in HDDs and TAC between nalmefene and placebo in the licensed population of the SENSE trial (adapted from table B22, p104 of the manufacturer's submission)

	Number of participants at baseline		Mean difference between nalmefene and placebo	95% CI	P value
	Nalmefene + PI	Placebo + PI			
Month 6	141	42	-2.6 HDDs/month	-5.5 to 0.2	0.071
			-15.3 g/day (TAC)	-29.1 to -1.5	0.031
Month 13	141	42	-3.6 HDDs/month	-6.5 to -0.7	0.016
			-17.3 g/day	-30.9 to -3.8	0.013
CI = confidence interval; DRL = drinking risk level; HDD = heavy drinking day; PI = psychosocial intervention; TAC = total alcohol consumption					

4.13 There manufacturer reported the results for a number of secondary endpoints in the 3 nalmefene trials. For conciseness only health-related

quality of life results measured by the EQ-5D are presented in this document.

4.14 The EQ-5D results from the ESENSE 1 and 2 trials demonstrated there was a statistically significant increase in scores for health state and utility index from baseline to month 6 when comparing nalmefene plus PI with placebo plus PI (see table 3).

Table 3. EQ-5D score mean change from baseline to month 6 in patients with high/very high DRL in the ESENSE 1 and 2 trials (adapted from table B19, page 102 of the manufacturer's submission)

Treatment group	Difference to placebo, mean (standard deviation)	95% CI, (p value)
ESENSE1		
Health state		
Nalmefene + PI vs. Placebo + PI	[redacted]	[redacted]
Utility index		
Nalmefene + PI vs. Placebo + PI	[redacted]	[redacted]
ESENSE2		
Health state		
Nalmefene + PI vs. Placebo + PI	[redacted]	[redacted]
Utility index		
Nalmefene + PI vs. Placebo + PI	[redacted]	[redacted]
CI = confidence interval; PI = psychosocial intervention		

4.15 When the results were pooled the mean change from baseline for nalmefene compared with placebo was 3.46 points (P = 0.0124) for the health state score and 0.03 points (P = 0.0445) for the utility index score. The Drinker Inventory of Consequences (DrInC) questionnaire was used to measure adverse consequences of alcohol abuse in five areas: interpersonal, physical, social, impulsive, and intrapersonal. When pooling the data from ESENSE 1 and 2 the mean DrInC was significantly correlated to HDD and TAC reduction (p<0.0001) with the manufacturer

suggesting fewer alcohol-related problems was significantly larger with nalmefene (17.86 ± 1.31) than with placebo (14.64 ± 1.30) (*P* = 0.0292).

4.16 The manufacturer did not perform a meta-analysis for the ESENSE 1, 2 and SENSE trial data but pooled the safety outcomes from all 3 trials and pooled the primary and secondary outcomes from ESENSE 1 and 2. There was no common treatment arm in the PI studies so an indirect meta-analysis could not be conducted between nalmefene and naltrexone. There were also concerns with the populations included in the studies and the applicability to England, with only 2 of the studies being conducted in the UK (Heather 2000, and UKATT 2005). Neither of these studies provided a relevant endpoint to be used to compare with outcomes from nalmefene studies.

Nalmefene compared with Naltrexone

4.17 As there were no direct head-to-head studies comparing nalmefene plus PI with naltrexone plus PI the manufacturer investigated whether a network meta-analysis or indirect comparison could be conducted. The manufacturer undertook a systematic review to identify studies evaluating nalmefene and naltrexone for reduction of alcohol consumption in actively drinking alcohol dependant people. The review identified 3 randomised controlled trials that compared oral naltrexone (50 mg/day) plus PI with placebo plus PI in actively drinking adults with alcohol dependence. The manufacturer stated that all the studies had limitations in the data reported meaning an indirect comparison could not be performed.

BRENDA (psychosocial intervention in ESENSE 1, ESENSE 2 and SENSE) compared with other types of psychological interventions

4.18 As there were no direct head-to-head studies comparing BRENDA with PI, as defined in NICE CG115, the manufacturer investigated whether a network meta-analysis or indirect comparison could be conducted. In order to identify trials investigating PIs listed in the final scope issued by NICE, for nalmefene, in addition to interventions listed in NICE CG115,

that were most similar to BRENDA, the manufacturer undertook a second systematic review. Based on the results of a survey conducted by the manufacturer of 20 primary care practices and specialist alcohol centres/addiction clinics from across England, the following PIs were included in the manufacturer's systematic search: cognitive behavioural therapies, behavioural therapies, social network and environment therapies, brief interventions and motivational enhancement therapy.

4.19 The literature search identified 7 studies on PI that met the inclusion criteria and which the manufacturer added to the 43 studies identified in NICE CG115. The manufacturer did not undertake a meta-analysis of the included studies it had identified (no explicit reasons were provided in the manufacturer's submission) but it did provide a summary of the absolute reductions in drinking that were provided in the PI trials. These trials showed that absolute reduction in total alcohol consumption from these studies range from 9.3 g/day to 50.7 g/ day, with a median value of 18.3 g/ day (range of follow-up time: 6 months to 12 months). The range was from 1.3 to 19, with a median value of 5.7 (range of follow-up time: 3 months to 12 months) for the absolute reduction of monthly HDDs. In the nalmefene trials, the absolute reduction in TAC in the nalmefene plus PI group ranged from 58.3 g/day to 70.4 g/day, whereas in the placebo plus PI group the absolute reduction in TAC ranged from 40 g/day to 60.1 g/day. The absolute reduction of monthly HDDs in the nalmefene plus PI group ranged from 11.6 to 12.9 whereas in the placebo plus PI group the absolute reduction of monthly HDDs ranged from 8 to 10.2 (range of follow-up time: 6 months to 12 months).

Adverse events

4.20 The SENSE trial was designed as a long-term safety study. The manufacturer also developed a safety database to input all data from the placebo and nalmefene groups from the 3 nalmefene trials. A pooled data set was produced to allow comparison of safety data between the 2 groups. The pooled data included all patients except those with no record

of treatment with a medicinal product. The frequency of the adverse events was defined as treatment-emergent adverse events with an incidence of ≥5% in either group. Incidences of adverse events for the nalmefene and placebo groups are shown below (see table 4 and 5). Frequent adverse events were of short duration in the total and licensed population, between 1 day (vomiting) and 7 days (nasopharyngitis) in patients treated with nalmefene.

Table 4. Treatment-emergent adverse events in the total population (taken from table B31, page 129 of the manufacturer's submission)

Adverse event	**Nalmefene + PI (n = 1,144)**	**Placebo + PI (n = 797)**
Patients with treatment-emergent AEs, n (%)	855 (74.7)	500 (62.7)
Nausea, n (%)	253 (22.1)	47 (5.9)
Dizziness, n (%)	208 (18.2)	44 (5.5)
Insomnia, n (%)	153 (13.4)	43 (5.4)
Headache, n (%)	141 (12.3)	66 (8.3)
Nasopharyngitis, n (%)	107 (9.4)	73 (9.2)
Vomiting, n (%)	100 (8.7)	18 (2.3)
Fatigue, n (%)	95 (8.3)	37 (4.6)
Somnolence, n (%)	59 (5.2)	23 (2.9)
AE = adverse event; DRL = drinking risk level; PI = psychosocial intervention.		

Table 5. Treatment emergent adverse events in the licensed population (taken from table B32, page 131 in the manufacturer's submission)

Adverse events	Nalmefene + PI (n = 475)	Placebo + PI (n = 369)
Patients with treatment-emergent AEs, n (%)	368 (77.5)	246 (66.7)
Nausea, n (%)	115 (24.2)	24 (6.5)
Dizziness, n (%)	104 (21.9)	22 (6.0)
Insomnia, n (%)	69 (14.5)	16 (4.3)
Headache, n (%)	60 (12.6)	35 (9.5)
Fatigue, n (%)	43 (9.1)	22 (6.0)
Vomiting, n (%)	40 (8.4)	13 (3.5)
Nasopharyngitis, n (%)	38 (8.0)	39 (10.6)
Sleep disorder, n (%)	32 (6.7)	4 (1.1)
Hyperhidrosis, n (%)	28 (5.9)	3 (0.8)
Decreased appetite, n (%)	27 (5.7)	4 (1.1)
Diarrhoea, n (%)	19 (4.0)	22 (6.0)
Accidental overdose, n (%)	13 (2.7)	22 (6.0)
AE = adverse event; DRL = drinking risk level; PI = psychosocial intervention.		

ERG Comments

4.21 The ERG commented that the manufacturer had undertaken a comprehensive systematic review and all relevant studies for nalmefene plus PI were included. Although the ERG was confident that no published studies for the comparator naltrexone were missed, during the manufacturer's review, it is unclear if all relevant data was included. No details were provided as to whether the manufacturer contacted the authors of the naltrexone studies to request additional unpublished data.

4.22 The ERG indicated that the post-hoc subgroup analyses of participants in the 3 nalmefene trials, that had high/very high DRL, may cause the efficacy and safety data to be less robust. The ERG stated that the studies were not powered for these post-hoc subgroups analyses and the effect of initial randomisation may have been lost. The ERG noted that a Scientific Advisory Group (SAG), which consulted the EMA during the nalmefene regulation process acknowledged that while post-hoc analyses are not ideal they are commonly used in trials for psychiatric drugs.

4.23 The ERG commented that the robustness of the evidence from the post-hoc subgroup analyses may also be affected by the high dropout rates in the 3 nalmefene trials. The EMA assessment report stated that the number of people who withdrew from the trials was comparable to that in other placebo-controlled studies conducted in patients with alcohol dependence. The manufacturer also undertook several sensitivity analyses to account for missing data but there were some inconsistencies as to whether statistical significance was achieved or not. The EMA noted a degree of uncertainty about the exact magnitude of benefit of nalmefene.

4.24 In the nalmefene trials, participants self-reported their alcohol intake, which the ERG indicated could bias the results. The manufacturer suggested that the timeline follow-back method used in the nalmefene trials is widely used in alcohol dependence trials and produces reliable retrospective self-reports of outpatient drinking.

4.25 The ERG indicated that the key uncertainties in the clinical evidence related to the types and frequencies of PI, along with its treatment duration and generalisability to England. PI in the form of BRENDA was used in the nalmefene trials but was delivered at different intervals to the PI (including behavioural therapies, cognitive behavioural therapy and behavioural couples therapies) recommended in NICE CG115. The ERG stated that it was difficult to know how the results would apply to people receiving different forms of frequencies of PI.

4.26 The 2 ESENSE trials treated participants for a duration of 6 months and the SENSE trial lasted for 12 months. The ERG stated that the safety and efficacy of nalmefene after 12 months is unknown and the Summary of Product Characteristics advises caution if nalmefene is prescribed for longer than 1 year.

4.27 The ERG had concerns about the generalisability of the population in the 3 nalmefene trials to clinical practice in England. The ERG commented

that the populations in the 3 nalmefene trials included participants who were predominantly white (>99%) with a mean age of 48 years in the ESENSE trials and 44 years in the SENSE trial. The ESENSE trials excluded participants with co-morbid psychiatric conditions and participants with severe psychiatric conditions were excluded from the SENSE trial. The manufacturer commented in its submission that many people with alcohol-dependence have diagnosed medical conditions and/or psychiatric comorbidities. The ERG stated that it was unsure if the study results can be extrapolated to a wider population. Participants 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 participants were from the UK (SENSE trial only, 5 sites out of a total of 60) and the manufacturer did not provide any data on the variability of the outcomes for different European countries. The ERG stated that the generalisability of this data for England was unknown.

5 Comments from other consultees

5.1 Clinical specialists indicated that alcohol dependence treatment varies widely over the UK in terms of service provision and treatments. The clinical specialists suggested that alcohol dependence can be treated in both primary and secondary care by both general and specialist staff involved. There are differences in opinion between professionals as to whether psychosocial or psychopharmacological treatments should be used. It was suggested by a professional group that nalmefene should be widely available and used within primary care and would be a useful treatment with patients who are heavy drinkers as there is little treatment available. It was advised that nalmefene should be widely publicised to make people aware of the treatment. The professional group considered general practitioners and nurses to be well placed to provide brief

interventions and motivational interviewing techniques. Additional resources would be required to deliver the interventions both in terms of staffing and cost of the intervention. The clinical specialists indicated that initially nalmefene may be started in specialist prescribing clinics with the associated costs of running these.

5.2 A clinical specialist suggested that although the technology may be useful for treating patients with a goal of controlled drinking, who currently have mild alcohol dependence, high drinking risk level but do not have physical withdrawal symptoms, it is not suitable for treating people who require immediate detoxification. Nalmefene is not suitable for patients taking opioid analgesia, those dependent on opioids or with previous history of severe withdrawals or significant liver/renal impairment which is a disadvantage of the treatment. The technology is already available in the UK but use varies across the country. There is also concern about limited UK experience of the drug and no direct clinical experience of its use so far. There may be issues with explaining to patients when to use nalmefene and also in working out which psychosocial intervention to use alongside. The clinical specialist commented that the trials excluded a number of people for whom the technology may be considered in routine clinical practice. The level of assessment and intervention may vary considerably from trial conditions. The trial outcome measures were considered to be internationally accepted standards in terms of HDD and TAC and have clinical applicability. The change in these over placebo will need to be considered in relation to whether this difference is clinically relevant. Longer term data would also be an advantage.

5.3 Nalmefene was considered by a patient group to be easily orally administrated on a daily basis. Another group suggested nalmefene allowed people to become abstinent and potentially improve other issues within the family whereas a second group thought nalmefene offered a new option for treating mild alcohol dependency. This could allow a period of respite for families and the stresses of living with someone who has a

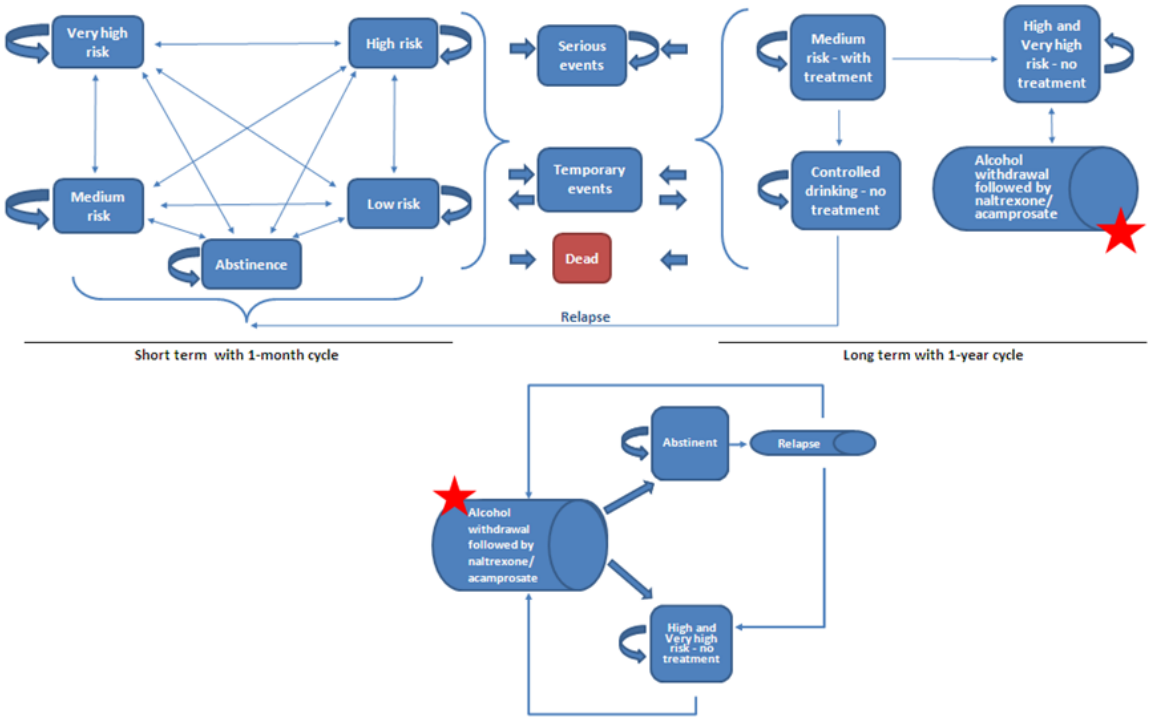
high drinking level and could help people who do not want to give up alcohol completely. One patient group suggested nalmefene is aimed at dependent drinkers who have psychological but not physical symptoms of withdrawal, which could be a large number of people. Patients living in stable accommodation with a caring family and friends could benefit more from the technology than those with a hectic life. There could also be a reduction in domestic violence and an improved outcome for children in the household, although these outcomes could be difficult to measure. One group suggested that only 6% of people currently access alcohol treatment and a new treatment may provide more options. If more people are treated it is possible to reduce both social and medical costs of alcohol. Nalmefene can also be given to patients who have advanced liver disease whereas other treatments such as naltrexone cannot. Patients waiting for a liver transplant have to stop drinking and nalmefene may enable them to do this. The main disadvantage, if the medication was not available on the NHS, would be the cost. Another disadvantage would be the requirement for a carer to supervise the consumption of the medication. Although no carer views on nalmefene had been documented the patient group did suggest that it may be similar to carers for people with a heroin addiction where they feel the person is ‘parked’ on methadone, potentially restricting recovery. One of the patient groups suggested that families, who have a member dependent on alcohol, can be stigmatised by society and this should be considered in the equalities of the evaluation. Another disadvantage could be the side effects of treatment highlighted in the clinical trials. A patient group suggested that if nalmefene is used along with psychosocial support in the correct patient group there may be no disadvantages to treatment.

6 Cost-effectiveness evidence

6.1 The manufacturer conducted a systematic review but did not identify any relevant cost-effectiveness studies for nalmefene in alcohol dependence. The manufacturer therefore conducted a *de novo* analysis to estimate the

cost-effectiveness of nalmefene compared with PI in treating patients with alcohol dependence. The manufacturer used a markov model which consisted of a short-term model (1 year based on the nalmefene clinical trials) with 1 month cycles and a long-term (up to 5 years using extrapolated trial results) model with 1 year cycles. The 1 year cycle aimed to take account of treatment efficacy and patient adherence and observed treatment discontinuation, incidence of alcohol-attributed harmful events and deaths. The 1 month cycle length was used to align with the patient follow-up in the trials (HDDs and TAC over 28 days). 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 manufacturer because there was available evidence for this length of time in terms of maintenance and recurrence of heavy drinking after initial response to treatment and second-line treatments. The 1 year cycle also reduced the number of assumptions and uncertainties the manufacturer considered it needed to use. Half-cycle correction was not incorporated because the manufacturer 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 and Wales, was from a NHS and PSS perspective and contained a discount of 3.5% was applied to utilities and costs. Figure 1 demonstrates the health states incorporated in the model.

Figure 1. Summary of the health states incorporated in the model (from manufacturer's submission)



6.2 The population in the model consisted of a cohort with alcohol dependence and defined drinking levels according to the WHO's definition of drinking-risk levels (see table 6). The model was developed based on the nalmefene clinical trials which used BRENDA as the PI.

Table 6. WHO 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

6.3 The analysis was based on pooled estimates from the 3 trials; ESENSE 1, 2 and SENSE, which included patients with high/very high DRL at screening and randomisation. Pooled primary efficacy endpoints (HDDs and TAC) of the 3 studies were used in the model (see tables 1 and 2 in

the clinical effectiveness section). Additionally the responder analysis was also pooled from the 3 studies. (odds ratio [OR] 1.55, 95% CI 1.06 to 2.25, p=0.0022).

6.4 The short-term time horizon of 1 year contained 5 drinking level health states which represent the health states defined by the WHO. Patients started in either the high or very high drinking level state in line with the indication for nalmefene. After the first year, 3 yearly health states were considered; controlled drinking, medium risk drinking and high/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. To account for the possibility that patients with controlled drinking may become heavy drinkers again a proportion of them were modelled to relapse at the end of the year and due to receive a second round of treatment. Patients who relapse, return to the same treatment in which they were initially successful in controlling alcohol intake (i.e. nalmefene plus PI or placebo plus PI). The proportion of patients who relapse 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. The patients in the medium risk drinking level group after 12 months were assumed to be responding to treatment but not enough to stop treatment completely. These patients can transition to either controlled drinking or high/very high risk drinking leading to a second-line treatment option. Patients in the high/very high risk drinking group after 12 months were presumed to have not responded to treatment and discontinue their current treatment. They were modelled to change treatment strategy to an abstinence-orientated/second-line approach which would include assisted alcohol withdrawal followed by acamprosate or oral naltrexone plus PI, to prevent relapse. In the model the secondary treatment sequence was accessed by a tunnel state based on the combined effect of alcohol withdrawal and acamprosate or oral naltrexone plus PI. Throughout the model patients can move to death at any point.

6.5 Patients who were in the medium risk drinking level at 12 months were assumed to have responded to treatment but not sufficiently to stop treatment altogether. These patients remained in the nalmefene plus PI or PI treatment groups, which according to the manufacturer's clinical specialists would align with clinical practice. This was modelled by extrapolating the latter 6 months of data from the SENSE trial. The average transition probabilities of the medium risk drinking level for the latter 6 months was used to model the yearly transition probabilities to either controlled drinking or high/very high drinking.

6.6 Several other assumptions were used both in developing the data and in the modelling. The manufacturer used clinical specialist opinion for inputs based on the number of GP and specialist care appointments a person would receive and the proportion of patients who would relapse and have a new round of treatment or relapse from secondary treatment. There was no evidence for the number of people who were likely to relapse so the model assumed the same number of people would relapse in both treatment arms regardless of drinking level. The length of temporary harmful events and the effects on costs and quality-adjusted life-years (QALYs) was decided in collaboration with public health experts while the more serious events were incorporated in absorptive health states.

6.7 The risk of a patient experiencing a harmful event was related to their WHO DRL. The harmful events included by the manufacturer were based firstly on those events that were costly to the healthcare system and had a strong evidence base. These events were also considered to be important by the manufacturer's clinical specialists and to occur in the 5 year time horizon included in the model. The harmful events were divided into 2 groups, immediate drinking (single episode) and continuous drinking events. If a patient experienced a serious event they were removed from the health state and the person stayed in a post event state for the duration of the model. The QALY for this cohort was then calculated based on the costs of the events, if the costs of the event were more than

the costs of alcohol treatment. Temporary events were modelled through tunnel states including costs and QALY decrements but no long-term effects were accounted for providing the person survived the tunnel state.

6.8 In the model an adverse event can cause the patient to change or dropout of treatment. Data on dropout rates was taken from the 3 pooled nalmefene trials. In the model, patients who experienced a nalmefene related event stayed in the nalmefene arm but received PI alone (modelled with the same transition probabilities as the PI arm), assuming the patient was still willing to undergo treatment. Patients who dropped out of treatment for reasons other than nalmefene side effects transition into the 'no treatment' group. These patients also went back to the high/very high WHO DRL group. No other pharmacological agent had been included as a comparator (see section 4.17) although the model does contain a secondary treatment option with the use of naltrexone or acamprosate to maintain abstinence.

6.9 In the model, the effect of second-line treatment with naltrexone or acamprosate was taken from the NICE CG115. The clinical guideline reviewed the available published data and used a mixed-treatment comparison to assess acamprosate plus PI and oral naltrexone plus PI for the treatment of alcohol dependency. The network meta-analysis showed that the probability of relapse to heavy drinking at 1 year was 0.8176 (95% CI 0.3894-0.9996) for acamprosate and 0.8253 (95% CI 0.4095-0.9997) for oral naltrexone. If patients were successful with treatment they moved to the abstinence health state but with a yearly probability that they may relapse.

6.10 A number of cost parameters were used in the model. For both treatment strategies included in the base-case analysis that is nalmefene plus PI and PI alone, the proportion of patients receiving treatment at a GP practice and at specialist level was set at 75% and 25% respectively. The number of consultations used in the nalmefene trials was applied to the

model, 3 visits in the first month and 1 per month after the first month. It was assumed that PI would be delivered during a consultation with the GP or specialist. These are shown in table 7 below.

Table 7. Costs parameters used in the model

Parameter	Nalmefene plus PI costs	PI costs
Nalmefene costs	£3.03 per tablet (average yearly cost £385 based on 127 days of medication)	NA
Visit to GP	£63 (17.4 minutes)	£63 (17.4 minutes)
First attendance at specialist care	£94	£94
Follow-up attendance at specialist care	£94	£94

6.11 The second-line treatment for assisted withdrawal using naltrexone or acamprosate had several costs attached dependent on the location of treatment; secondary care outpatient-assisted withdrawal £606, home-based assisted withdrawal (£596) or secondary care inpatient-assisted withdrawal (£4145). These costs were used to calculate a weighted average cost (using 2009/2010 costs and estimates of alcohol dependency from NICE CG115). The average cost of PI was also taken from the NICE clinical guideline and was the mean costs of the 3 main types of therapy: cognitive behavioural therapies, behavioural therapies or social network, and environment-based therapies. The cost for behavioural therapies was estimated by NICE CG115 to be £741 (one 60-minute session per week for 12 weeks). The NICE clinical guideline also estimated the cost of pharmacological intervention (acamprosate or oral naltrexone), along with the additional monitoring needed when these drugs are prescribed, to be £431. Therefore relapse treatment costs were £1172 (£431 + £741).

6.12 The model also took into account societal costs related both to crime and productivity as specified in the remit from the Department of Health (see section 3.1). The inclusion of a societal perspective was taken account of

in scenario analyses and was not included in the manufacturer's base-case. Data from the Sheffield Alcohol Policy Model (Sheffield University, 2009), which assessed the effectiveness and cost-effectiveness of public health-related strategies and interventions to reduce alcohol-attributable harm in England, was used to incorporate costs in the model. The alcohol consumption used to model the increased risk of crime was based on the average drinking level (HDD) rather than TAC as there is no delay in time.

6.13 Utility weights were obtained from the EQ-5D questionnaire (see sections 4.13 and 4.14) 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 scores for the cost-effectiveness model. Two sets of utility weights were incorporated in the model for each drinking health state. The first set was calculated using the area under the curve for the nalmefene and placebo groups, using pooled EQ-5D data from each data collection point during the trials. This represented a QALY gain over 1 year for each treatment arm of the nalmefene trials. The second set of utility values were derived from the 3 nalmefene trials using pooled utility analysis for 'abstinence and low risk' and 'high and very high risk' as there was little difference in the utilities between the drinking levels in these groups. In the base-case the first set of data was used and for years 2 to 5 of the base-case analysis the second set of pooled utility data was applied. In addition to these analyses, an alternative source of utility weights from a disease management study of people with alcohol dependence in the UK primary care setting was also used (STREAM study). Health-related quality of life data for people experiencing a harmful event was taken from the Health Outcomes Data Repository (HODaR) collected in the Cardiff and Vale Hospital Trust in Wales. The Sheffield Alcohol Policy Model used this data to retrieve utility data (Sheffield University, 2009) which were used in the model. This data set did not include utility scores for respiratory infections so a targeted review was

performed by the manufacturer to identify utility values for this health state.

6.14 The manufacturer's base-case results showed that nalmefene plus PI dominated PI alone (see table 8).

Table 8. Manufacturer's Base-case result (taken from table B79, page 239 of the manufacturer's submission)

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs (95% CI)	Incremental LYG (95% CI)	Incremental QALYs (95% CI)	ICER
PI (standard care)	£4,842	4.404	3.553				
Nalmefene + PI	£4,445	4.413	3.624	−£397 (−£1,068 to £81)	0.009 (0.005 to 0.018)	0.071 (0.042 to 0.141)	Nalmefene dominates. Probability of cost-effectiveness £20k and £30k is 100%

ICER = incremental cost-effectiveness ratio; LYG = life-years gained; PI = psychosocial intervention; QALYs = quality-adjusted life-years.

6.15 One-way sensitivity analysis was performed with 232 parameters tested which corresponds to all the parameters except the transition probabilities. The parameters that had the most effect on the cost-effectiveness of the treatments were the number of medical visits per month (for both treatments), the proportion having treatment following relapse, the utility value used and the cost of nalmefene. Nalmefene plus PI remained cost-effective when varying all parameters except altering the number of medical visit per month. When applying the upper bound for this parameter, the ICER increased to £6274 (see table 9). The results of the probabilistic sensitivity analysis showed that the uncertainty around all parameters included in the model was not influencing the conclusion of the base-case analysis.

Table 9. The change in ICER caused by adjusting individual parameters (taken from table B80, page 240 of the manufacturer's submission)

Parameter	ICER at lower bound	ICER at upper bound	Mean value (range tested)
Medical visits per month nalmefene	−£11,495	£6,274	1 (0.5-2)
Medical visits per month for PI treatment	−£425	−£15,867	1 (0.5-2)
Utility – Area under the curve from ESENSE & SENSE PI	−£3,734	−£10,976	0.81 (0.77-0.85)
Utility – Area under the curve from ESENSE & SENSE nalmefene	−£8,561	−£4,130	0.83 (0.8-0.86)
Probability of relapse	−£7,652	−£3,682	0.19 (0.1-0.19)
Number of visits first month for nalmefene treatment	−£8,083	−£4,317	3 (1-4)
Cost of nalmefene	−£7,316	−£3,829	3.03 (2.42-4)
Number of visits first month for PI treatment	−£3,331	−£6,693	3 (1-4)
QALY: abstinence	−£6,613	−£4,815	0.86 (0.84-0.86)
Discount rate: cost	−£6,666	−£4,898	4 (0-0.06)
Cost: other injury	−£4,740	−£6,405	5296.01 (3220.01-7372.05)
QALY: very high risk	−£4,894	−£6,469	0.79 (0.77-0.81)
Proportion of day at risk of other accidents (hours)	−£4,817	−£5,917	3 (1-4)
Cost of visit to GP	−£6,084	−£5,060	63 (38-87.7)
Discount rate: outcomes	−£5,028	−£5,975	3.5 (0-0.06)
Proportion of visits to GP (to specialized care)	−£4,929	−£5,786	0.75 (0-1)
Male RR other injury	−£5,281	−£6,030	2.19 (1.7-2.19)
Male RR mortality due to cirrhosis of the liver	−£5,737	−£5,125	1.69 (1.32-1.69)
Cost of follow-up attendance to specialized care	−£5,809	−£5,335	94 (57-131)
Female RR other injury	−£5,398	−£5,846	2.19 (1.7-2.19)
Base-case analysis	**−£5,574**		

6.16 Scenario analysis testing the impact of varying the time horizon, assuming nalmefene intake on every day that the patient was in the model, perspective on cost, utility data used, and removing the second-line treatment option, was performed. Eight different scenarios were tested by the manufacturer and the results are shown in table 10.

- Scenario 1: Time horizon reduced to 1 year
- Scenario 2: Societal perspective included
- Scenario 3: Time horizon reduced to 1 year and societal perspective included
- Scenario 4: Nalmefene intake assumed to be every day rather than as needed
- Scenario 5: No second-line treatment options are allowed
- Scenario 6: Using utility values from the STREAM study81
- Scenario 7: A threshold analysis increasing the treatment effect of PI relative to nalmefene in addition to PI to identify the level of efficacy required to have a cost per QALY of £20,000 and of £30,000.
- Scenario 8: An assumption that PI was associated with zero costs

Table 10. Summary of results of the scenario analyses (taken from table B21, page 243 of the manufacturer's submission)

Scenario	Incremental costs (£)	Incremental LYs	Incremental QALYs	Cost/QALY (£)
Scenario 1	£408	0.002	0.017	£24,684
Scenario 2	-£2,893	0.009	0.071	Nalmefene dominates
Scenario 3	-£95	0.002	0.017	Nalmefene dominates
Scenario 4	£21	0.009	0.071	£289
Scenario 5	£438	0.012	0.086	£5,090
Scenario 6	-£397	0.009	0.192	Nalmefene dominates
Scenario 7	NA			
Scenario 8	£576	0.071	0.071	£8,088

6.17 Following a request for clarification by the ERG and NICE the manufacturer corrected a minor error in the model and presented further scenario analyses which the ERG termed Scenario 9 and 10. Scenario 9

provided an ICER for the use of PI as suggested by NICE CG115 with 1 session of PI lasting 60 minutes per week for 12-weeks. Scenario A increased the costs of PI alone whereas Scenario B assumed the cost increase for PI applied to both nalmefene plus PI and PI alone (see table 11).

Table 11. Scenario analysis 9 assuming 1 60 minute session of PI per week for 12 weeks (taken from table 40, page 109 of the ERG report).

Scenario	Total costs		Total QALYs		Incremental costs	Incremental QALYs	ICER
	NMF + PI	PI alone	NMF + PI	PI alone			
Base-case	£4,445	£4,842	3.624	3.553	-£397	0.071	Nalmefene + PI dominates
Scenario A	£4,445	£5,933	3.624	3.553	-£1,488	0.071	Nalmefene + PI dominates
Scenario B	£4,874	£5,933	3.624	3.553	-£1,059	0.071	Nalmefene + PI dominates
NMF: Nalmefene; PI: Psychosocial Intervention							

6.18 Scenario 10 assessed alternative assumptions for the treatment pathway of patients at a medium risk level after 12 months. There were 3 scenarios; the first assuming patients relapse after 12 months to high or very high drinking risk level and the second assumed patients had responded to treatment and was modelled in line with other patients who responded. The third scenario assumed patients in the nalmefene plus PI arm did not respond to treatment but those in the PI alone arm did respond. For the first 2 scenarios nalmefene plus PI still dominated PI alone whereas for the third scenario the cost per QALY was £6280 when comparing nalmefene plus PI with PI alone.

ERG Comments

6.19 The ERG thought the manufacturer's model was generally well constructed and had few errors.

6.20 The economic model did not include a half-cycle correction. The ERG acknowledged that the impact of half-cycle correction in the monthly time

cycle was likely to be small but that omitting half-cycle correction in the yearly cycles was a limitation. A more accurate estimation would be obtained by assuming that all events took place midway through the year rather than occurring at the start of the year.

6.21 Within the model the PI component was assumed to be represented by BRENDA as employed in the 3 nalmefene trials (see sections 4.4, 4.18 and 4.19). The ERG noted that BRENDA contrasts strongly with NICE CG115. The ERG stated that the evaluation undertaken in the model does not meet that specified in the final scope issued by NICE which specified that the comparator should be PI (as defined in NICE CG115). The manufacturer assumed that BRENDA would be performed by GPs on 75% of occasions with the remaining 25% performed at specialist level. The ERG stated that its clinical advisors disagreed with this assumption stating that the proportion undertaken in specialist care would be much higher were best practice followed; NICE clinical guideline states that' all interventions for people who misuse alcohol should be delivered by appropriately trained and competent staff'.

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

6.23 The transition probabilities used for abstinent and low risk drinking levels were based on data from 30 years ago (Taylor et al.) and the ERG questioned the generalisability to 2014. The manufacturer estimated the number of people who would relapse from abstinence or low risk drinking level to be 19% and that they would return to high or very high drinking levels in the same proportions as at the beginning of treatment (42.5% and 57.5% respectively). The ERG considered these assumptions

inaccurate for 2 reasons. The first because the original source of the data (Taylor et al.) was only based on a proportion of people in the study (68 of 99 people) and secondly the possibility of the patient regressing to a less severe drinking state had not been included. The ERG was unsure whether this assumption was favourable or unfavourable to nalmefene. Transition probabilities for the medium risk drinking level were taken from the SENSE trial but without the raw data the ERG could not calculate whether the figures were accurate.

6.24 The ERG stated that its clinical advisors 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 advisors believed that GPs would not let patients drink at very high risk levels for greater than 6 months without recommending intensification of treatment and additional specialist input, and that 3 months might be a more likely cut off point. The ERG highlighted that this issue was raised with the manufacturer during the clarification process and that the manufacturer maintained that the 12 months duration was appropriate as the patients were initially only mildly dependent with no features of withdrawal. The ERG stated that this issue remained an area of disagreement, and that the manufacturer provided no evidence as to why the people all meet the criteria for medically assisted withdrawal at 12 months rather than at 60 months. The ERG also stated that this issue will add uncertainty to the cost-effectiveness ratio, although it is not clear whether such changes would be favourable or unfavourable to nalmefene.

6.25 The manufacturer assumed that 12.5% of people received inpatient medically assisted withdrawal, 43.75% received outpatient medically assisted withdrawal and 43.75% received home based medically assisted withdrawal. The costs assumed by the manufacturer were taken from NICE CG115. The ERG stated that its clinical advisors thought that the proportion of people receiving medically assisted withdrawal as an inpatient was too high given the characteristics of the population entering

the model. The ERG commented that if this was the case then the assumptions made by the manufacturer would be favourable to nalmefene.

6.26 There were no costs or health-related quality of life reduction explicitly associated with the adverse events. The manufacturer assumed that costs were negligible and disutility was captured in the EQ-5D but nalmefene plus PI and PI alone had the same utility values per drinking state. The ERG commented that nalmefene specific adverse events were not appropriately captured and this would favour nalmefene.

6.27 The ERG noted a slight error in the manufacturer's PSA analysis because the percentage of patients who would be treated by a GP had a deterministic value of 75% but the probabilistic value was uniform between 40% and 60%. When the ERG amended this distribution to a uniform 65% to 85% it made little difference to the results.

6.28 The ERG also commented that in the manufacturer's base-case there were more unfavourable than favourable assumptions used in the model. Unfavourable assumptions included: a time horizon of 5 years, the assumption that age and gender matched mortality rates are applicable to the population in the decision problem and those that have had a serious or temporary event; that only one serious event was permitted; that drinking risk levels were considered irrelevant after a serious event; using the lower bounds and uninflated costs of a medically assisted withdrawal. The favourable assumptions to nalmefene included: over-estimation of rates of serious and temporary events; the over-estimation of crime rates, although not in the base-case; the high (in the opinion of the clinical advisors to the ERG) proportion of patients receiving medically assisted withdrawal as an inpatient; the assumption that all patients would require medically assisted withdrawal if they remained at high or very high risk levels at 12 months; that drug wastage was not included in the base-case; 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.

6.29 The ERG had a number of concerns regarding the scenario analyses undertaken by the manufacturer. The manufacturer carried out 8 scenarios analyses with one of the scenarios including when medically assisted withdrawal was not allowed (Scenario 5). The clinical advisors to the ERG thought the assumption which led to this scenario, that all patients that were still high or very high drink risk level after 12 months would receive medically assisted withdrawal, would be unlikely. The ERG was also unsure as to the reasons behind Scenario 8 (assumption that PI was associated with zero costs) as nalmefene is only indicated to be prescribed with PI, which incurs costs. A typographical error was also noted in Scenario 8 with respect to life years which the ERG believed should be equal to those in Scenario 1 (time horizon reduced to 1 year). The ERG was unable to replicate the cost results for Scenario 8. For Scenario 7 the manufacturer assumed the efficacy between nalmefene plus PI and PI alone would have to reduce by 70.3% to have a cost per QALY of £20,000 and reduced by 77.2% to have a cost per QALY of £30,000. In response to clarification, the manufacturer stated that it did not think that Scenario 7 was realistic, but the clinical advisors to the ERGs were less certain that such a conclusion could be drawn.

6.30 The ERG believed that a major limitation of Scenario 9 was that PI and nalmefene plus PI were assumed to have the same efficacy and that these analyses were therefore invalid. The ERG suggested the correct analysis would be to increase the costs of PI and undertake the threshold analysis as in Scenario 7. Scenario 9B also lacked face validity with the costs of PI alone increasing markedly more than nalmefene plus PI. The clinical advisors to the ERG were also concerned that Scenario 9A could be misinterpreted to suggest that the PI regime in the NICE guidance was not necessary.

6.31 The ERG stated that the largest limitation of the manufacturer's cost-effectiveness analysis was that no formal comparison was performed between nalmefene plus PI and PI alone where PI was that included in the NICE CG115.

ERG's exploratory analyses

6.32 The ERG stressed that the decision problem cannot be fully evaluated within the currently available data. The ERG noted that 4 comparisons could be formulated with the robustness of the estimates of nalmefene plus PI cost-effectiveness decreasing as the comparisons become more relevant to the decision problem (see table 12).

Table 12. The 4 comparisons formulated by the ERG

Comparison	Definition
Comparison 1	The analysis of the cost-effectiveness of the addition of nalmefene to a PI of lower intensity than recommended in NICE CG115
Comparison 2	A threshold analysis which estimates the reduction in the benefit associated with nalmefene necessary to reach cost per quality adjusted life years (QALY) of £20,000 and £30,000
Comparison 3	The manufacturer did not comment on the likely cost-effectiveness of delayed initiation of nalmefene for those who did not respond to PI as recommended in NICE CG115 compared with immediate initiation of nalmefene for all patients. Delayed use of nalmefene would be aligned with the recommendation for pharmacotherapy in NICE CG115, although this guideline was written before the licensing of nalmefene.
Comparison 4	The manufacturer 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 CG115.

ERG's exploratory analyses in Comparison 1

6.33 The ERG undertook a number of exploratory analyses and carried out some deterministic sensitivity analysis. These analyses were amendments of the manufacturer's base-case except that it was assumed that those drinking to a medium drink risk level at 12 months had relapsed to a high/very high drink risk level (Manufacturer's Scenario A of Scenario Analysis 10). The exploratory analyses conducted are listed below;

1. Impact of patients withdrawing from nalmefene due to adverse events also withdrew from PI. Two scenarios were run, the first assumed all

patients withdrawing from nalmefene withdrew from PI and the second presume 50% of the patients also withdrew from PI

2. Assumed 50% of patients received outpatient medically assisted withdrawal and 50% received this treatment at home
3. Assumed 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
4. The cost of a specialist PI appointment was £119 rather than £94 in accordance with more recent data
5. Assumed that the utility for patients on nalmefene plus PI and for PI alone were equal in the first year although the ERG did not deem this plausible

6.34 The ERG's base-case included points1, 2 and 5, with the assumption that 50% of people withdrawing from nalmefene would also withdraw from PI treatment. In the ERG base-case, nalmefene plus PI still dominated PI alone. The ERG carried out a second analysis but presumed no second-line treatment options were allowed and the ICER was £5166 per QALY gained when comparing nalmefene plus PI to PI alone. Although the ERG was critical of the fact that the manufacturer did not conduct half-cycle correction the model was not adapted by the ERG to allow this for 2 reasons; the first was the time required 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 two arms apart from those drinking at medium drink risk levels; and that any potential inaccuracy was relatively small compared with the uncertainty within Comparisons 2 and 3.

ERG's exploratory analyses in Comparison 2

6.35 For comparison 2 the ERG suggested it unlikely that people at medium risk drinking level would be treated indefinitely and assumed in comparison 1 that these people would relapse to high and very high risk levels. The ERG was unable to undertake threshold analysis altering the variable treatment options because this part of the model was not

functioning and given the impact in the ICER was small the ERG left the assumption as it was. The threshold analysis undertaken by the manufacturer in Scenario 7 was re-assessed by the ERG using its Scenario 1 (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 manufacturer. If the efficacy of nalmefene and PI compared with PI alone were reduced by 62.8% then the cost per QALY would become £20,000. The reduction would have to be 71.5% for the cost per QALY to reach £30,000. The ERG suggested that the lack of half-cycle correction and duration of which patients stayed in the high to very high risk level would affect these results. Analyses taking into account the cost of crime indicated that the reduction would need to be 80.4% for the cost per QALY of the addition of nalmefene to be £20,000 and be 83.1% for the cost per QALY to be £30,000.

ERG's exploratory analyses in Comparison 3

6.36 For comparison 3 the ERG highlighted that there was little data to assess the cost-effectiveness of nalmefene with PI when using PI as described in NICE CG115. The time point at which PI alone was not successful was also unknown but the nalmefene trials indicated that when patients were treated with BRENDA alone, 20% were either abstinent or of low risk drinking level. The ERG suggested a greater response may be seen with higher intensity PI and that the costs of nalmefene can be saved without incurring health losses particularly if nalmefene use is delayed. The ERG did caution that there would be uncertainty about the efficacy of nalmefene in patients who had not responded to PI alone.

ERG's exploratory analyses in Comparison 4

6.37 For comparison 4 again the ERG suggested there was little data available and therefore did not feel comfortable estimating an ICER for this comparison.

7 Equality issues

7.1 There could be issues with consent of treatment in certain populations in terms of cognitive decline and learning disability.

8 Innovation

8.1 Both the professional group and clinical specialist considered nalmefene to be novel because it supports a reduction in drinking rather than abstinence. It could provide a treatment for patients who do not currently receive treatment.

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Appendix A: Supporting evidence

Related NICE guidance

Published

- Psychosis with coexisting substance misuse. NICE clinical guideline [120](2011)
- Alcohol-use disorders: diagnosis, assessment and management of harmful drinking and alcohol dependence. NICE clinical guideline [115] (2011)
- Alcohol-use disorders: diagnosis and clinical management of alcohol-related 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)
- Alcohol dependence and harmful alcohol use quality standard. NICE quality standards [11] (2011)

NICE pathways

- There is a NICE pathway on Alcohol-use disorders, which is available from http://pathways.nice.org.uk/pathways/alcohol-use-disorders

Appendix B: Clinical efficacy section of the draft European public assessment report

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002583/WC500140326.pdf