Nalmefene for reducing alcohol consumption in people with alcohol dependence: A Single Technology Appraisal

Errata

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subsequent treatment with naltrexone or acamprosate, although this option could be removed within the model.

For Comparison 1 the manufacturer estimated that nalmefene and PI dominated PI, that is nalmefene and PI was cheaper and more effective than PI alone; the conclusion that nalmefene plus PI was more cost-effective than PI alone was robust in all sensitivity analyses undertaken. For Comparison 2, the manufacturer estimated that the benefit of adding nalmefene to low-intensity PI would need to be reduced by 70% to obtain a cost per QALY of £20,000 and by 77% to obtain a cost per QALY of £30,000. No comments on the cost-effectiveness of nalmefene in addition to PI in Comparisons 3 or 4 were provided by the manufacturer.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG considered the model submitted by the manufacturer to be generally well-constructed with the majority of assumptions being unfavourable, rather than favourable, to nalmefene, although half-cycle correction was not undertaken. In the model it was assumed that all patients who failed to respond to nalmefene and PI would need medically assisted withdrawal from alcohol which the clinical advisors to the ERG considered unlikely and hence inappropriate. There was no allowance within the model for these individuals to receive additional specialist input and hence it is unclear how the incorporation of such specialist input at an earlier time would impact on the cost-effectiveness of nalmefene. [Text Deleted]. The largest limitation was that no formal comparison of nalmefene plus PI compared with PI alone, where PI was that recommended by NICE CG115.

1.6 ERG commentary on the robustness of evidence submitted by the manufacturer

1.6.1 Strengths

The manufacturer undertook a comprehensive systematic review (no major limitations were noted) of nalmefene for the reduction of alcohol consumption in people with alcohol dependence. The ESENSE1, ESENSE2 and SENSE trials were of reasonable methodological quality (with some limitations) and measured a range of clinically relevant outcomes.

The mathematical model submitted by the manufacturer had few errors and appeared well-constructed. The manufacturer acknowledged that the PI undertaken in the RCTs did not meet the requirements recommended in NICE CG115 and undertook a threshold analysis to assess the level of reduction in the efficacy benefit required to produce cost per QALY values of £20,000 and £30,000.

1.6.2 Weaknesses and areas of uncertainty

The pivotal RCTs of nalmefene in addition to PI compared with PI alone use PI in the form of BRENDA which is less intensive than PI recommended in NICE CG115. The small number of UK

who are alcohol dependent, brief interventions are less effective and referral to a specialist service is likely to be necessary (Moyer *et al*., 2002[13]). It is important, therefore, that health and social care professionals are able to identify and appropriately refer harmful drinkers who do not respond to brief interventions, and those who are alcohol dependent, to appropriate specialist services.'

3) That currently pharmacological intervention would be considered for use in patients with mild alcohol dependence only in those who had not responded to PI or those who have specifically requested a pharmacological intervention (Section 7.16.5 of NICE CG115). The ERG acknowledges that NICE CG115 was written before nalmefene was licensed, but notes that it is a plausible strategy that nalmefene, in those who have not requested a pharmacological intervention, be reserved for those who have not adequately responded to PI. A clinical advisor to the ERG stated that a possible reason as to why PI is recommended first-line in CG115 is that the techniques recommended can change a person's approach to their addiction problem and hence their behaviour. The clinical advisor stated that PI can equip people with coping skills which can be called on in the future to help maintain abstinence whereas a pharmacological interventions per se would not affect the patient's behaviour when the treatment is discontinued.

The implications of these statements for this Single Technology Appraisal (STA) will be discussed later in the document at appropriate points.

For a patient whose condition worsens to such a level that detoxification is required NICE CG115 recommends that patients with moderate and severe alcohol dependence should have an immediate treatment goal of abstinence; these patients should undergo detoxification via a medically assisted alcohol withdrawal programme. After successful completion of the alcohol withdrawal programme, the physician may consider pharmacotherapy together with ongoing PI to assist in maintaining abstinence. In these cases the manufacturer assumed that treatment with naltrexone, acamprosate or disulfiram could be provided.

The diagram of current service provision as provided by the manufacturer (Figure A4, p45 of the MS) is replicated in Figure 3 and the manufacturer's proposed placement of nalmefene in the service pathway (Figure A5, p46 of the MS) is reproduced in Figure 4. It can be seen that the use of nalmefene is proposed only for those who are still drinking at high-risk levels two weeks following a brief intervention. The manufacturer only appraises two alternatives, namely nalmefene plus PI, and PI alone: there is no consideration of nalmefene being provided only to non-responders to PI, or consideration of naltrexone being used prior to medically assisted withdrawal. One of the clinical advisors to the ERG commented that the 'treatment objectives not met box' would not necessarily

Table 4: Characteristics of included studies

Study	Country (sites)	Design	Population	Interventions	Comparator	Primary outcome measures	Duration
ESENSE1 (Study 12014A)[28-30]	Austria (n=4), Finland (n=11), Germany (n=16), and Sweden (n=8)	Phase III randomised, double-blind, placebo-controlled, parallel-group trial (n=604)	Patients aged ≥ 18 years (recruited from in- and out- patient clinics) with a primary diagnosis of alcohol dependence according to DSM-IV-TR criteria; ≥ 6 HDDs, an average alcohol consumption at WHO medium risk level or above or ≤ 14 abstinent days in the 4 weeks preceding the screening visit	Oral nalmefene 18 mg (fixed daily dose tablet, as-needed use) plus PI [a] (n=306)	Placebo (matching tablet, as-needed use) plus PI [a] (n=298)	Change from baseline in the monthly number of heavy drinking days[b] and total alcohol consumption (g/day)[c] at month 6.	6 months
ESENSE2 (Study 12023A)[29,31,32]	Belgium (n=7), Czech Republic (n=3), France (n=16), Italy (n=10),	Phase III randomised, double-blind, placebo-controlled,	Patients aged ≥ 18 years (recruited from in- and out- patient clinics) with a primary diagnosis of alcohol dependence	Oral nalmefene 18 mg (fixed daily dose tablet, as-needed use)	Placebo (matching tablet, as-needed use) plus PI [a]	Change from baseline in the monthly number of heavy drinking days[b] and total alcohol consumption (g/day)[c]	6 months

Study	Country (sites)	Design	Population	Interventions	Comparator	Primary outcome measures	Duration
	Poland (n=7), Portugal (n=4), and Spain (n=10	parallel-group trial (n=718)	according to DSM-IV-TR criteria; ≥ 6 HDDs, an average alcohol consumption at WHO medium risk level or above or ≤ 14 abstinent days in the 4 weeks preceding the screening visit	plus PI [a] (n=358)	(n=360)	at month 6.	
SENSE (Study 12013A)[32-34]	Czech Republic (n=5), Estonia (n=5), Hungary (n=2), Latvia (n=4), Lithuania (n=2), Poland (n=15), Russia (n=8), Slovakia (n=4), Ukraine (n=10), and the UK (n=5)	Phase III, randomised, double-blind, placebo-controlled, parallel-group trial (n= 675)	Patients aged ≥ 18 years (recruited from outpatient clinics) with a primary diagnosis of alcohol dependence according to DSM-IV-TR criteria; ≥ 6 HDDs, an average alcohol consumption at low risk level or above or ≤ 14 abstinent days in the 4	Oral nalmefene 18 mg (fixed daily dose tablet, as needed use) plus PI [a] (n=509)	Placebo (matching tablet, as-needed use) plus PI[a] (n=166)	Long-term safety and tolerability (adverse events, clinical safety laboratory tests and vital signs) Change from baseline in the monthly number of heavy drinking days[b] and total alcohol consumption (g/day)[c] at month 6.	52 weeks

Study	Country (sites)	Design	Population	Interventions	Comparator	Primary outcome measures	Duration
			weeks preceding the screening visit				

DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; HDD, heavy drinking days; PI, psychosocial intervention

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

[b] Defined as a day with alcohol consumption ≥ 60 g for men and ≥ 40 g for women.

[c] Defined as mean daily alcohol consumption in g/day over a month (28 days).

men and women (aged over 18 years) with a DSM-IV-TR diagnosis of alcohol dependence and at least six heavy drinking days in the preceding 28 days. The people included had an average daily alcohol consumption level conferring low risk or higher or ≤ 14 abstinent days in the 4 weeks preceding the screening visit. Individuals with a history of delirium tremens, withdrawal symptoms requiring medication (a Revised Clinical Institute Withdrawal Assessment for Alcohol Score ≥10), liver function abnormalities (aspartate aminotransferase and/or alanine aminotransferase >3 times the upper reference limit), blood alcohol concentration >0.02% and severe medical conditions were excluded; however, people with psychiatric comorbidities such as depression, anxiety, social phobia and insomnia, were included.

Similar to the ESENSE studies, the SENSE trial had an initial 1- to 2-week screening period, after which patients were randomised 3:1 to 52 weeks of as-needed treatment with nalmefene plus PI or placebo plus PI. A safety follow-up visit was scheduled for 4 weeks after completion of the study or after withdrawal from the study. All PI sessions (BRENDA) were provided by trained personnel and were delivered at weekly intervals for the first 2 weeks and monthly thereafter. The co-primary outcome measures included: long-term safety and tolerability and changes from baseline in the number of heavy drinking days per month and total alcohol consumption at month six. In the 1−2 weeks between screening and randomisation, a large proportion of people reduced their alcohol intake to less than six heavy drinking days per month or below a medium drinking risk level (39% [215/552, full analysis set] and no longer fulfilled the pre-specified inclusion criteria.[34] In addition, during the main treatment period after randomisation, 37% (243/665) of people withdrew from the study (38% [191/501] and 32% [52/164] for nalmefene-treated and placebo-treated participants, respectively)[34] leading to missing data, which may have affected the statistical analyses. As described later the manufacturer used multiple imputation methods to address this issue. The post-hoc subgroup efficacy analyses, as per the licensed population, included 183 participants (full analysis set) who had a high or very high drinking risk level at both screening and randomisation.

- *Ongoing studies of nalmefene (p32, MS)*

Several ongoing studies were noted in the MS; however, detailed study characteristics (including expected completion dates) were lacking. A summary of relevant studies, as reported in the MS (p32), for the use of nalmefene in people with alcohol dependence is summarised in Table 5.

Figure 6: Total alcohol consumption (g/day) – conventional pairwise meta-analysis of changes from baseline to Month 6: Licensed population[a]

Table 8: Total alcohol consumption (g/day) – pooled analysis (using patient level data adjusted by country) of changes from baseline to Month 6: Licensed population[a]

Treatment Group	Change from baseline to Month 6 (g/day)		Difference to placebo		
	N	Mean ± SE	Mean ± SE	95% CI	p-value
Pooled studies: ESENSE1, ESENSE2, SENSE					
Nalmefene plus PI					
Placebo plus PI					

CI, confidence interval; PI, Psychosocial Intervention, [a] Full analysis set using a mixed model repeated measures approach

Secondary outcomes

A range of secondary efficacy endpoints were reported in the MS (p94-105) including the following: responder analysis based on various drinking measures (e.g. a downward shift from baseline in WHO drinking risk levels by two risk categories and reduction from baseline in monthly total alcohol consumption); alcohol dependence symptoms and clinical status (change from baseline in Clinical Global Impression –Improvement [clinician assessed] Scale, Clinical Global Impression-Severity Scale and Drinker Inventory of Consequences Score); liver function test results (serum-gamma-glutamyl transferase and serum-alanine amino transferase activities); and quality of life measures (SF-36 and EQ-5D). Where pooling of data was pre-specified, the manufacturer undertook pooled analyses based on individual patient data (measures which included responder analysis, SF-36, EQ-5D and the Drinker Inventory of Consequences total score). Where pooling was not undertaken, outcomes data were reported for each individual study. A detailed rationale for the different approaches was not provided in the MS. For detailed results refer to p94-105 of the MS and Appendix 4 of the manufacturer's clarification response to question B6.

Table 13: Treatment-emergent adverse events with an incidence of ≥ 5% in either treatment group: Total population (Data derived from p130 of the MS and clarification response to question B19)

Adverse event	ESENSE1		ESENSE2		SENSE		Pooled	
	Nalmefene + PI (n=302)	Placebo + PI (n=296)	Nalmefene + PI (n=341)	Placebo + PI (n=337)	Nalmefene + PI (n=501)	Placebo + PI (n=164)	Nalmefene + PI (n=1144)	Placebo + PI (n=797)
Patients with treatment-emergent adverse events	246 (81.5%)	198 (66.9%)	232 (68.0%)	199 (59.1%)	377 (75.2%)	103 (62.8%)	855 (74.7%)	500 (62.7%)
Nausea	83 (27.5%)	18 (6.1%)	58 (17.0%)	20 (5.9%)	112 (22.4%)	9 (5.5%)	253 (22.1%)	47 (5.9%)
Dizziness	83 (27.5%)	23 (7.8%)	52 (15.2%)	15 (4.5%)	73 (14.6%)	6 (3.7%)	208 (18.2%)	44 (5.5%)
Insomnia	30 (9.9%)	10 (3.4%)	49 (14.4%)	22 (6.5%)	74 (14.8%)	11 (6.7%)	153 (13.4%)	43 (5.4%)
Headache	36 (11.9%)	27 (9.1%)	43 (12.6%)	26 (7.7%)	62 (12.4%)	13 (7.9%)	141 (12.3%)	66 (8.3%)
Nasopharyngitis	34 (11.3%)	37 (12.5%)	19 (5.6%)	17 (5.0%)	54 (10.8%)	19 (11.6%)	107 (9.4%)	73 (9.2%)
Vomiting	24 (7.9%)	8 (2.7%)	19 (5.6%)	8 (2.4%)	57 (11.4%)	2 (1.2%)	100 (8.7%)	18 (2.3%)
Fatigue	53 (17.5%)	25 (8.4%)	NR	NR	27 (5.4%)	3 (1.8%)	95 (8.3%)	37 (4.6%)
Somnolence	NR	NR	NR	NR	42 (8.4%)	8 (4.9%)	59 (5.2%)	23 (2.9%)
Sleep disorder	32 (10.6%)	1 (0.3%)	NR	NR	NR	NR	NR	NR
Hyperhidrosis	16 (5.3%)	5 (1.7%)	NR	NR	NR	NR	NR	NR
Decreased appetite	NR	NR	NR	NR	26 (5.2%) [a]	2 (1.2%) [a]	NR	NR
Diarrhoea	NR	NR	8 (2.3%)	17 (5.0%)	NR	NR	NR	NR
Accidental overdose	NR	NR	NR	NR	9 (1.8%) [a]	9 (5.5%) [a]	NR	NR
Fall	NR	NR	NR	NR	7 (1.4%) [a]	11 (6.7%) [a]	NR	NR

PI, Psychosocial Intervention, NR, not reported
[a] Data from Van den Brink *et al*.[34]

4.3.2 *Psychological/psychosocial intervention (p108-127, MS)*

In the absence of direct head-to-head studies comparing BRENDA with PI (as defined in NICE CG115),[3] the manufacturer investigated whether a network meta-analysis or indirect comparison could be undertaken. As a result, the manufacturer conducted a systematic review to identify clinical trials investigating the use of PI (as listed in the final scope issued by NICE, for nalmefene, in addition to interventions listed in NICE CG115[3] that were most similar to BRENDA) in alcohol dependence. The review updated an existing review of psychosocial comparators that was undertaken to inform NICE CG115,[3] within the context of the manufacturer's systematic review.

The manufacturer's systematic review used a similar approach to that of the nalmefene and naltrexone reviews they had conducted. As the current review was an update of an existing review, all searches were limited by date from September 2009 (last search date, including six month overlap, from earlier review) to December 2013 and English language (further details on search limitations are provided in Section 4.1.1). However, details on how the update was conducted were lacking (e.g. details of data extraction and quality assessment of included studies from the existing review) in the MS. Eligible studies included adults with alcohol dependence. The PI interventions (as specified in the final scope issued by NICE including interventions listed in NICE CG115[3] that were most similar to BRENDA [the psychosocial treatment used in the three nalmefene trials]) included: extended brief interventions and motivational techniques; however the manufacturers also looked at: cognitive behavioural therapies; behavioural therapies; motivational enhancement therapy; and social network and environment therapies. Drinking outcomes that were considered relevant included the following: level of alcohol consumption; number of drinks per day; and number of heavy drinking days or percentage of heavy drinking days.

Initially, the manufacturer's systematic review identified 50 potential RCTs. Of these, 43 were identified from the original NICE review and 7 were identified by the updated searches (further details are provided in Table B28, p121-123 of the MS). On further assessment, only 22 studies met the manufacturers systematic review inclusion criteria (motivational techniques, n=5; cognitive behavioural therapies, n=12; behavioural therapies, n=4; and social network and environment based therapies, n=1). Although poorly reported, the ERG assumes that all the excluded studies failed to provide details on relevant outcome data e.g. total daily alcohol consumption and change in number of heavy drinking days. In addition, as noted in the manufacturer's clarification response to question B17, no attempt was made by the manufacturer to contact authors of these excluded PI studies to request potential additional unpublished data.

Although a meta-analysis of the included studies was not undertaken by the manufacturer (no explicit reasons were provided in the MS) a summary of the absolute reductions in drinking that were reported

Temporary events comprised: lower respiratory tract infections; transport-related injuries; and injuries not related to transport. Contrary to the assumptions made following a serious event the drinking risk level of the patient was maintained alongside the temporary health states. Patients experiencing temporary events incur an additional cost and a HRQoL decrement but do not discontinue treatment. Temporary events are modelled as tunnel states and patients may experience more than one temporary event within the model time horizon although not simultaneously. As detailed later, the risks of experiencing a temporary event increases as does the drinking risk severity.

Patients may die at any point in the model. The mortality rate was assumed to be comprised of three distinct elements: mortality associated with experiencing a serious event; mortality associated with experiencing a temporary event; and background mortality associated with other causes, the rates of which were set to that for the age- and gender-matched general population. Experiencing a non-fatal serious or non-fatal temporary event in previous time cycles did not influence the underlying mortality rate. These assumptions are likely to be unfavourable to nalmefene although this impact is reduced to the short time horizon of the model.

The model allows patients to discontinue treatment as observed in the RCTs. Patients who discontinued treatment due to nalmefene-related adverse events such as: nausea; dizziness; insomnia; or headaches were assumed to switch to PI alone. The assumption that patients who experience a nalmefene-related adverse event continue with PI rather than discontinue treatment may be favourable to nalmefene. The manufacturer did not consider that such patients could receive off-label naltrexone as a replacement intervention; it is unclear if this were modelled whether this would be favourable or unfavourable to nalmefene. No costs of adverse events are included in the model with the manufacturer assuming the costs were negligible. In the first year it was assumed that the utility recorded in the RCTs captured the adverse events, however the ERG comment that the utility data did not use any imputation for missing data. Beyond the first year, both the nalmefene plus PI and PI alone treatments use the same utility values per drinking state, which will be favourable to nalmefene as nalmefene-specific adverse events would be appropriately captured.

Patients who discontinue treatment for non-nalmefene related reasons were assumed to receive no further treatment and to immediately transition to either the very high-risk drinking level state (57.5%) or the high-risk drinking level state (42.5%) with these proportions being those assumed at model entry for the population. Patients receiving no treatment are assumed to remain in their allocated drinking risk level, for the remainder of the initial year.

At the end of the initial 12 months patients are divided into three drinking risk groups: abstinent or low-risk; medium-risk; or high- or very high- risk.

manufacturer estimated that the undiscounted costs of PI alone for a person who does not drop out would be 14 x (£63 x 0.75 + £94 x 0.25) or £991 per annum, although the total would be greater if a larger proportion of patients were treated in specialist care centres. More recent costs, using a different methodology than those used by the manufacturer have been reported by the Personal Social Services Research Unit. The cost of a face-to-face contact with a specialist prescriber for drug misuse is reported to be £119 and has been used by the ERG in sensitivity analyses.[78]

The manufacturer states that 'The Department of Health has approved a UK nalmefene price of £3.03 per tablet', which if the drug is taken every day would add an additional £1107 per annum. The manufacturer states that in 'the pivotal clinical trials, the observed case analysis showed that patients took medication an average of 127 days per annum. With a cost per patient based on nalmefene costing £3.03 per tablet, the average cost of nalmefene would be £385 per year. According to the primary statistical mixed model repeated measures analysis, patients took medication on an average of 56% of days (204 days),' which the ERG has calculated would be a cost of £620 for a full year of nalmefene. Drug wastage, by not completing a full pack, was not explicitly included by the manufacturer although a scenario analysis was undertaken in which nalmefene was assumed to be taken every day rather than as required. No monitoring costs, for example increased liver function tests, were included in the model, although the clinical advisors to the ERG did not see this as a large limitation given the low price of such tests, and that only a small proportion of patients would receive these in the nalmefene plus PI arm, but not in the PI arm alone.

Within the mathematical model the average nalmefene use per month was subdivided into sex and drinking risk levels. These data are replicated in Table 27. The ERG comments that those patients in the abstinent group were still taking nalmefene tablets which may be contrary to the nalmefene SPC which states that 'If you and your doctor have decided that your immediate goal is abstinence (not drinking any alcohol), you should not take Selincro because Selincro is indicated for reduction of alcohol consumption'.[14]

Table 27: Average nalmefene intake per month by sex and drinking risk level

	Average Intake per month (20mg tablets)	
Drinking Risk Level	Males	Females
Very High	20.47	19.12
High	19.89	18.89
Medium	16.54	16.46
Low	13.92	14.82
Abstinent	8.80	7.71

5.2.7.2 Costs of medically assisted withdrawal

The manufacturer assumed that 12.5% of patients received inpatient medically assisted withdrawal, 43.75% received outpatient medically assisted withdrawal and 43.75% received home-based medically assisted withdrawal (see NICE CG115 for definitions). The costs assumed by the manufacturer were taken (and assumed to remain at 2009/10 prices) from NICE CG115[3] which were between £4145 and £6175 for each patient receiving inpatient medically assisted withdrawal, £606 for each patient receiving outpatient medically assisted withdrawal, and between £596 and £771 for those receiving home-based medically assisted withdrawal. The manufacturer used the lower estimate of the range in both instances which is unfavourable to nalmefene, producing a weighted average of £1404 per patient receiving medically assisted withdrawal.

The proportion of patients receiving medically assisted withdrawal as an inpatient was thought to be too high by the clinical advisors to the ERG given the characteristics of the population entering the model; if this was the case then the assumptions made by the manufacturer would be favourable to nalmefene.

5.2.7.3 Costs of serious and temporary events

The costs for serious and temporary events were stated as being largely taken from a report written by the University of Sheffield.[75] The ERG comments that the actual reference for these costs are Appendix 5 of the University of Sheffield report. [79] The values used by the manufacturer were those reported in the 'Total cost per person-specific hospitalisation' column divided by the 'Multiplier' value. These represent hospitalisation costs only and thus ongoing costs, for example for patients who have had a stroke, are not considered. This omission is likely to be unfavourable to nalmefene. Distributions on these costs were estimated assuming that the standard error was 20% of the mean. The one exception was the costs of lower respiratory infection, which was not included in the University of Sheffield report. These data were stated to be taken from NHS Reference Costs, with a distribution estimated assuming that the standard error was 20% of the mean, although no reference was provided to check the mean values. All prices were inflated to 2011/2012.[77] These data are reproduced in Table 28.

[Text Deleted and column removed for Table 28]

Table 28: Costs associated with adverse events used by the manufacturer

Event	Mean value used in the model	Distribution used in the model	Distribution parameters used in the model
Heart disease	£2,491	Gamma	α = 25 ß = 99.658
Ischaemic stroke	£4,088	Gamma	α = 25 ß = 163.525
Haemorrhagic stroke	£5,799	Gamma	α = 25 ß = 231.956
Cirrhosis of the liver	£3,750	Gamma	α = 25 ß = 150.008
Pancreatitis	£4,373	Gamma	α = 25 ß = 174.903
Lower respiratory infection	£2,999	Gamma	α = 25 ß = 119.974
Injury associated with transport	£5,468	Gamma	α = 25 ß = 218.733
Injury not associated with transport	£5,296	Gamma	α = 25 ß = 211.84

[a] Assumed to be alcoholic liver disease [b] Assumed to be road traffic accidents - non pedestrian

[c] Assumed to be Fall injuries N/A – Not available

5.2.7.4 The costs of crime

The costs of the set of crimes that are an option for inclusion in the model are detailed in Table 29, which replicates Table B65 on p225 of the MS. These values have been calculated with monetary values placed on the lost health gains. As such only costs are included in the model with no further health decrement modelled. The validity of this method has been questioned by Rittenhouse[80] where the ICERs estimated when health effects are monetised and included in the numerator rather than transformed into QALYs and included in the denominator.

Table 29: The unit costs of crime assumed in the model

Crime	**Cost**
Causing death by dangerous driving	£1,794,890
More serious wounding	£26,354
Less serious wounding	£9,911
Assault on a constable	£1,772
Assault without injury	£1,772
Criminal damage	£1,065
Theft from a person	£1,038
Robbery	£8,959
Robbery (business)	£6,151
Burglary in a dwelling	£4,020
Burglary not in a dwelling	£3,322
Theft of a pedal cycle	£780
Theft from vehicle	£1,056
Aggravated vehicle taking	£5,091
Theft of vehicle	£5,091
Other theft	£780
Theft from shops	£123
Violent disorder	£12,803
Sexual offences	£38,676
Homicide	£1,794,890

5.2.8 Utilities

5.2.8.1 Utilities associated with drinking risk levels in the first year

The utility associated with each drinking risk level were obtained from EQ-5D questionnaire administered in the three RCTs (ESENSE1[28], ESENSE2[31], SENSE[32]). In two of these trials (ESENSE1, ESENSE2) the EQ-5D questionnaire were administered at baseline, week 12 and week 24 and in the remaining trial (SENSE) EQ-5D questionnaires were administered at baseline, week 12, week 25, week 36 and week 52.

The area under the curve was estimated at every three months from baseline to one year (adjusted for the baseline utility, and assuming a linear transition between the mean utilities at each time point). The manufacturer states in response to clarification question C5 that "this method of applying utilities from a clinical trial was informed by NICE CG100 and has the advantage of being able to capture the disutility of adverse events relating to nalmefene." However, this approach may have limitations since data from people who dropped out, or data that was otherwise missing, were not imputed, as stated in the manufacturer's response to clarification question C6. Given the relative frequency of dropout the lack of imputation may be favourable to nalmefene in the initial year.

Table 30: Utility data derived from the ESENSE1, ESENSE2 and SENSE RCTs

Description	Mean value	Distribution	Parameters
Utility associated with drinking risk levels			
Very high or high	0.79	Beta	α = 1310 ß = 348
Medium	0.82	Beta	α = 1210 ß = 266
Low or abstinent	0.86	Beta	α = 1035 ß = 168

An alternative source was also considered for estimating utility data. These were from a naturalistic disease management study (STREAM study) of patients with alcohol dependence in the UK primary care setting at the GP level.[81] These values are provided in Table 31 and have lower midpoint utility levels per drinking risk level than in the base case, and also greater uncertainty in the values.

Table 31: Utility data derived from the STREAM Study

Description	Mean value	Distribution	Parameters
Utility associated with drinking risk levels			
Very high	0.531	Beta	α = 65 ß = 57
High	0.609	Beta	α = 74 ß = 48
Medium	0.714	Beta	α = 53 ß = 21
Medium	0.755	Beta	α = 96 ß = 31
Low or abstinent	0.816	Beta	α = 40 ß = 9

5.2.8.3 Utilities associated with serious and temporary events

The utility values associated with each serious or temporary event are detailed in Table 32. All values were taken from a report undertaken by the University of Sheffield.[79] The original source did not assume uncertainty in these values, and in order to include these variables within PSA the manufacturer assumed a standard error of the mean of 0.02 and fitted a beta distribution to the values.

Table 36: Base case deterministic results presented by the manufacturer

Treatment	Total costs	Total QALYs	Incremental costs	Incremental OALYs	ICER
PI	£4,842	3.553			
Nalmefene + PI	£4,445	3.624	-£397	0.071	Dominating

PSA was undertaken with the results provided in Table 37. These were generated from 5000 sample configurations. The manufacturer used non-informative priors (of 0.1) to facilitate the derivation of beta distributions for transition probabilities where there were zero observed counts. A slight error was noted in the PSA analysis regarding the population of the percentage of patients who would be treated by a GP as the deterministic value was 75%, however, the probabilistic distribution was uniform between 40% and 60%. Amending this distribution to a uniform (65%, 85%) made little difference to the results and therefore for transparency reasons the results presented in the MS rather than amended results have been reported in Table 37.

The ERG comment that in the manufacturer's base case there are more unfavourable assumptions to nalmefene than favourable assumptions, although the magnitude of these assumptions combined are unknown. Unfavourable assumptions included: [Text Deleted]; 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 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; 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 fact that nalmefene-related adverse events were not incorporated in terms of costs throughout the model and disutilities beyond the initial year; and that the utility data in year 1 were not adjusted for missing data.

Table 37: Base case probabilistic results presented by the manufacturer

Treatment	Total costs	Total QALYs	Incremental costs	Incremental OALYs	ICER
PI	£5,220	3.535			
Nalmefene + PI	£4,760	3.621	-£460	0.087	Dominating

5.2.9.3 Scenario analyses undertaken by the manufacturer

The manufacturer undertook eight scenario analyses. These are described below with explicit reference to the changes from the base case.

- 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 study[81]
- 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

The results for these scenarios analyses (excluding Scenario 7) are shown in Table 39. This is essentially a replication of Table B81 (page 243 of the MS). The largest mean cost per QALY value generated in the scenario analyses was slightly below £25,000 and occurred when the modelling horizon was limited to a one year period. This is unfavourable to nalmefene and PI which resulted in more people being in less severe drinking states at month twelve, (as shown in Figure 14 and Figure 15), who would be assumed to generate no benefit in terms of health or savings. Four of the scenarios estimated that nalmefene would not be cost-saving. These scenarios include when medically assisted withdrawal was not allowed indicating that this has a marked effect of costs; the clinical advisors to the ERG thought that the present assumption that all patients received medically assisted withdrawal at 12 months if they were still in a high- or very high-risk level is unlikely to be correct.

The rationale for Scenario 8 is unclear, as nalmefene is only indicated to be prescribed in conjunction with continuous PI focused on treatment adherence and reducing alcohol consumption and the forms of PI recommended in NICE CG115[3] certainly incur costs. There is a presumed typographical error in Scenario 8 with respect to life years, which the ERG believes should be equal to those in the manufacturer's base case. Furthermore the ERG could not replicate the cost results for Scenario 8, and it is unclear why there has been a much larger drop in the PI alone arm, despite PI being included in both arms.

The results from Scenario 7 are shown in Figure 18 which is a reproduction of Figure B29 on page 244 of the MS. This indicates that the efficacy difference between nalmefene and PI and PI alone

who did not respond to PI; in all cases PI is that as recommended in NICE CG115. The use of off-label naltrexone for 'people with mild alcohol dependence who have not responded to PI alone, or who have specifically requested a pharmacological intervention' is recommended in NICE CG115.

5.3.1 The exploratory ERG analyses in Comparison 1

The ERG undertook a number of exploratory analyses which are detailed below. These analyses are amendments of the manufacturer's base case except that it was assumed that those drinking to a medium-risk level at 12 months had relapsed to a high- / very high-risk level. (Scenario A of Scenario Analysis 10.)

Deterministic results are provided for each individual exploratory analysis. Probabilistic analyses were not undertaken although the ERG notes that this may be unfavourable to nalmefene based on the results provided in Table 42.

The exploratory analyses conducted by the ERG are bulleted below. The results from the exploratory analyses undertaken are provided in Table 42.

- [Text Deleted]
- Assuming that the utility in year 1 was equal for those in the malmefene plus PI arm and the PI alone arm. This is not deemed plausible but assesses the impact of this on the ICER.
- Assessing the impact if patients withdrawing from a nalmefene-related adverse event also withdrew from PI. Two scenarios were run assuming all patients that had a nalmefene-related adverse event withdrew from PI and assuming that 50% of those with a nalmefene-related adverse event withdrew from PI
- Assuming that 50% of patients received outpatient medically assisted withdrawal and 50% received home-based medically assisted withdrawal. Using the midpoint of the range from NICE CG115 this equated to a cost per medically assisted withdrawal of £645.
- Assuming that the costs of serious and temporary events were zero and that the utility was the same as for those drinking at a very high-risk level. This is not deemed plausible but assesses the impact of these variables on the ICER.
- That the cost of a specialist prescribing face-to-face contact was £119 rather than £94 in accordance with more recent data.

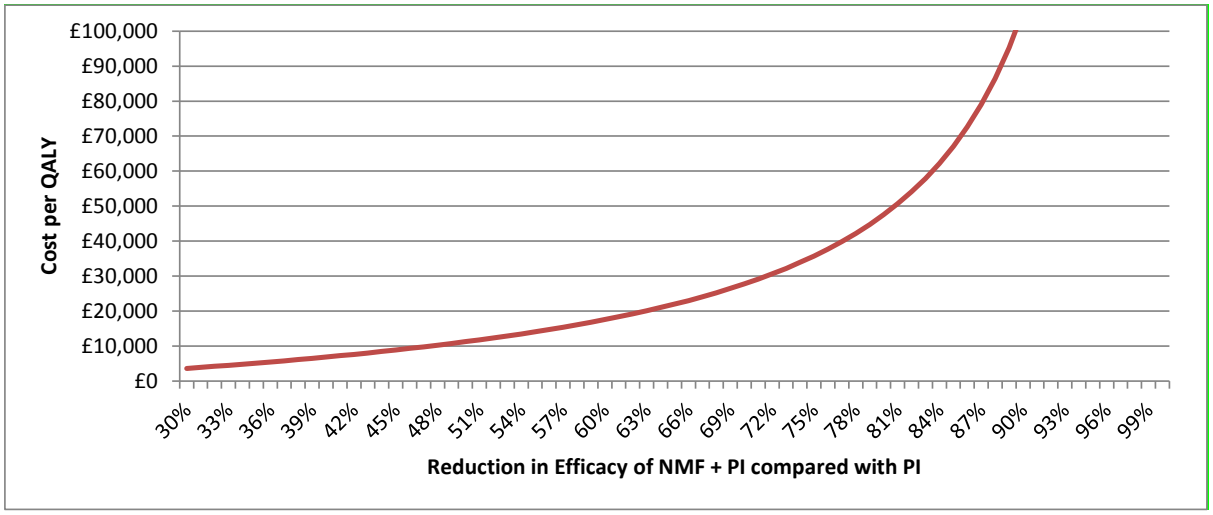
The ERG base case incorporated each of the points above, with the assumption that 50% of those patients who had a nalmefene-related adverse event would also drop-out from PI based on clinical advice provided to the ERG. An additional analysis was undertaken on the ERG base case to examine

Table 42: Exploratory Analyses undertaken by the ERG in Comparison 1

Code	Change from MS base case	Total costs		Total QALYs		Incremental costs	Incremental QALYs	ICER
		NMF + PI	PI alone	NMF + PI	PI alone			
MS base case	-	£4,445	£4,842	3.624	3.553	-£397	0.071	NMF + PI dominates
1	Medium-risk drinkers assumed to relapse to high- / very high-risk	£4,803	£5,240	3.608	3.538	-£437	0.070	NMF + PI dominates
2	Utility for NMF + PI and for PI alone set to 0.82 in the first year	£4,445	£4,842	3.613	3.558	-£397	0.055	NMF + PI dominates
3	All patients who withdraw for NMF-related reasons also withdraw from PI	£4,685	£4,842	3.607	3.553	-£157	0.055	NMF + PI dominates
4	Half of patients who withdraw for NMF-related reasons also withdraw from PI	£4,565	£4,842	3.616	3.553	-£277	0.063	NMF + PI dominates
5	Assuming an average cost of medically assisted withdrawal of £645 per patient	£4,186	£4,438	3.624	3.553	-£253	0.071	NMF + PI dominates
6	Costs of specialist prescribing face to face contact set to £119	£4,560	£4,945	3.624	3.553	-£385	0.071	NMF + PI dominates
7	Costs of serious or temporary events set to £0 and associated utility set to that of very high-risk drinkers.	£3,625	£3,811	3.685	3.623	-£186	0.062	NMF + PI dominates
ERG Base Case	1 + 4 + 5 + 6	£4,624	£4,849	3.601	3.538	-£226	0.063	NMF + PI dominates
ERG Base Case but no second-line treatment options are allowed		£2,954	£2,578	3.528	3.455	£377	0.073	£5,166

NMF: Nalmefene; PI: Psychosocial Intervention

Figure 19: Threshold analysis undertaken by the ERG regarding the efficacy of nalmefene and PI compared with PI alone



The results produced by the ERG are similar to those produced by the manufacturer in that 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 comment that the uncertainties in the ICER regarding the lack of half cycle correction and the duration for which patients would be allowed to remain in the high- / very high-risk level also apply to these results. Additionally the threshold values were calculated using deterministic results which may be unfavourable to nalmefene. 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.

Additional analyses including costs of crime and justice were undertaken, albeit with the caveat that the methodology used may not be valid. In this circumstance 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.

5.3.3 The exploratory ERG analyses in Comparison 3

There are very few appropriate data to assess the cost-effectiveness of nalmefene with PI as recommended in NICE CG115 with PI as recommended in NICE CG115 supplemented with nalmefene in those that did not have a positive response to PI. The evaluation is also made more complex by the time point at which PI alone is assumed to have not been successful is not defined. Data from the pivotal trials indicate that approximately 20% of patients had low-risk drinking levels or were abstinent at month 3 on BRENDA alone. It is expected that a greater response rate would be observed were higher intensity PI as recommended in NICE CG115 used. The ERG believe it