London New Drugs Group / London Medicines Evaluation Network Review

Nalmefene for alcohol dependence

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Summary

- Nalmefene (Selincro®), is an opioid receptor modulator which is licensed for the reduction of alcohol consumption in adult patients who continue to have a high drinking risk level 2 weeks after initial assessment, without physical withdrawal symptoms and who do not require immediate detoxification. Nalmefene should be prescribed in conjunction with continuous psychosocial support.
- Three pivotal phase 3 clinical trials, supported by subgroup analyses in the licensed population, have shown that, when compared to placebo, as-needed nalmefene significantly reduced the total number of heavy drinking days and total alcohol consumed by more than half. All trial participants received psychosocial support.
- This effect was most pronounced in the subgroup of patients (just over 50%) who had a high drinking risk level both at screening and 2 weeks after the initial assessment, before any medication was started. The license was therefore restricted to this group as patients who reduced their drinking in the 2 weeks following screening gained little additional benefit.
- Nalmefene costs £3.03 per tablet making the annual prescribing costs an estimated £553, per patient if the drug is taken on an average of 50% of the days. The annual drug costs per 100,000 population might be between £13,475 and £19,355 depending on how often the drug is taken and assuming an uptake rate of 20%.

1. Background and introduction

Nalmefene is dual-acting opioid system modulator, with a distinct μ-, δ- and κ- receptor profile. The proposed mechanism of action is to restore the balance of a dysregulated motivational system by reducing the reinforcing effect of alcohol, and thereby reducing the urge to drink alcohol. (1-6) Nalmefene, was launched in the UK, in May 2013 based on the results of three phase 3 clinical trials. Two of these trials were 6 months in duration, and the third lasted 12 months. In April 2013, revised subgroup analyses of these studies were published in poster form. (5,6,7) These post-hoc subgroup analyses looked at data from approximately 850 patients, who continued to have a high drinking risk level (>60g/day, or 7.5 units for men and >40g /day or 5 units for women) 2 weeks after the initial assessment. The post-hoc subgroup analyses, of the two six month trials, were fully published in July 2013 and it was these which informed the licensed indication. (8)

Guidelines and alternative treatments

NICE published guidance on alcohol use disorders in 2011. (9) Treatments for alcohol dependence include pharmacological and/or psychological/psychosocial therapy for the management of withdrawal symptoms and the prevention of relapse. People with mild dependence usually do not require assisted alcohol withdrawal. People with moderate to severe alcohol dependence will usually need assisted alcohol withdrawal, with treatment options including psychological as well as pharmacological interventions. People with moderate to severe dependence can typically be managed in the community; however those with previous complications, e.g. delirium tremens (DTs) or seizures, may require management in a residential setting. (9,10,11)

In October 2013 the Scottish Medicines Consortium (SMC) accepted the use of nalmefene within NHS Scotland. (12) The detailed advice from the SMC can be found at:
http://www.scottishmedicines.org/files/advice/nalmefene_selincro)FINAL_September_2013_website.pdf The incidence and prevalence of alcohol dependence varies across the UK and is much higher in Scotland than in England.

Current treatment options include:

For mild alcohol dependence: psychological intervention (such as behavioural therapies or social network and environment-based therapies) focused specifically on alcohol-related cognitions, behaviour, problems and social networks.

For moderate to severe alcohol dependence:

- psychological intervention.
- assisted withdrawal: benzodiazepines; chlordiazepoxide, diazepam or oxazepam or second line; chlormethiazole.
- relapse prevention (in combination with psychological intervention); acamprosate, disulfiram, naltrexone.

Associated treatments for assisted withdrawal may include high potency vitamin supplementation (e.g. Pabrinex), and the use of medications for symptomatic relief e.g. loperamide and analgesics. There is commonly also a need for the concurrent treatment of psychiatric complications. (10,11)

2. Proposed place in therapy

Nalmefene is licensed for the reduction of alcohol consumption in adult patients with alcohol dependence who have a high drinking risk level; ≥60g (7.5 units) per day for men and ≥40g (5 units) per day for women, without physical withdrawal symptoms and who do not require immediate detoxification. Nalmefene should only be prescribed in conjunction with continuous psychosocial support focused on treatment adherence and reducing alcohol consumption and should only be initiated in patients who continue to have a high drinking risk level two weeks after initial assessment. The license was restricted to patients with a continued high drinking risk level 2 weeks after assessment because patients who reduced their drinking in the initial 2 weeks, due to non-pharmacological interventions, consumed so little alcohol that there was little room for further significant improvement (floor effect). (1)

3. Evidence selected for inclusion

The marketing authorisation for nalmefene was supported by data from three multi-country European phase 3 clinical trials ESENSE 1 (2), ESENSE 2 (3) and SENSE (4) enrolling approximately 2,000 patients in total. These studies compared its effect on alcohol consumption by the monthly number of heavy drinking days defined as ≥60g per day for men and ≥40g per day for women, and monthly total alcohol consumption g/day, against treatment with placebo. The number of heavy drinking days and total alcohol consumption were assessed and reported by the patients. The monthly drinking variables were derived from the 'Timeline Follow-Back' method that provided information on daily number of standard drinks. A conversion card was provided to define 'standard drinks' and the conversion of a 'standard drink' to 'grams' was performed by a statistical programmer taking into account country specific factors. In both arms of the studies all patients were given the same psychosocial support programme. ESENSE 1 and ESENSE 2 are fully published and SENSE is available in abstract/poster form only. In addition, post-hoc subgroup analyses of these three trials, looking at the effect of nalmefene in the specific licensed patient population only, have been presented and published in poster form (5,6,7) together with a fully published subgroup analysis of ESENSE 1 and 2. (8)

ESENSE 1 was a 6 month, randomised, double blind, placebo-controlled, parallel group study in 604 adults (placebo n=298, nalmefene n=306), mean age 51.6 years, (67% men). For the co-primary outcome, nalmefene was significantly superior to placebo in reducing the number of heavy drinking days (-2.3 days/month [95% CI: -3.8 to -0.8]; *p=0.0021*) and total alcohol consumption (-11.0 g/day [95% CI: -16.8 to -5.1]; *p=0.0003*) at month 6 when compared to placebo. The mean number of heavy drinking days in the nalmefene group decreased from 19 to 8 days/month, and the mean total alcohol consumption decreased from 84g to 33g per day. In the placebo group, the mean number of heavy drinking days decreased from 20 to 11 days per month and the mean total alcohol consumption decreased from 85g to 45 g per day at month 6. On average, patients in the placebo group took the study medication on nearly two thirds of the days and patients in the nalmefene group on almost half of the days. Withdrawal rates were high and during the main treatment period, 160 (53%) of the nalmefene treated patients and 91 (31%) of the placebo treated patients dropped out of the study. This dropout rate was significantly different between the two groups (*p < 0.0001*). The most common reason was withdrawal of consent in the placebo group and adverse events (AEs) in the nalmefene group. AEs were generally transient and mild or moderate. (2)

ESENSE 2 was identical in design to ESENSE 1, included 718 adults (placebo n=360, nalmefene n=358), mean age 44.8 years, (73% men). With regard to the two primary end points, at month 6, nalmefene was statistically superior to placebo in reducing heavy drinking days (group difference: -1.7 days/month [95% CI -3.1; -0.4]; *p=0.012*) but did not achieve a statistically significant reduction in total alcohol consumption (group difference: -5 days last month [95% CI -10.6; -0.7]; *p=0.088*). The mean number of heavy drinking days in the nalmefene group decreased from 20 to 7 days per month, and the mean total alcohol consumption decreased from 93g to 30g per day. In the placebo group, the mean number of heavy drinking days decreased from 18 to 8 days per month and the mean total alcohol consumption decreased from 89g to 33g per day at month 6. Adverse events were more common in the nalmefene group however; the incidence of adverse events leading to withdrawal was at the same level as placebo. (3)

Subgroup analysis of ESENSE 1 and ESENSE 2

In this paper, the pooled target population as specified in the licence, which consisted of 667 patients, (n=335 in the nalmefene group and n=332 for placebo) were analysed. This group was chosen because in both the 6 month studies (2,3) a large improvement was seen in the first 2 weeks between screening and the start of treatment (18% in ESENSE 1 (2) and 33% in ESENSE 2 (3)). In these patients there was little room for further improvement when they were then treated with nalmefene or placebo.

In the subgroup of patients who continued to have a high drinking risk level 2 weeks after screening (58% of the total ESENSE 1 and 46% of the total ESENSE 2 population) there was a superior effect of nalmefene compared with placebo in reducing the number of heavy drinking days [treatment difference: -3.2 days/month (95% CI: −4.8; −1.6); *p<0.0001*] and total alcohol consumption [treatment difference: −14.3 g/day (−20.8; −7.8); *p<0.0001*] at month 6. In the nalmefene group, the number of heavy drinking days reduced from 23 to 10 after 6 months, a reduction of 55%. This compared with a reduction from 22 to 13 days in the placebo group, a reduction of 42%. Total alcohol consumption decreased from 107.7g per day to 42.0g per day after six months in the nalmefene group, a reduction of 61%. This compared with a change from 103.3g per day to 51.9g per day in the placebo group, a decrease of 50% at month 6. On average, patients on placebo took study medication on 72% of the days in the main treatment period, whereas patients on nalmefene took study medication on 58% of the days. Overall adverse events and adverse events leading to dropout were more common with nalmefene than placebo. The AEs with the highest incidences were central nervous system and gastrointestinal events, which had higher incidences in the nalmefene group than in the placebo group and reflect antagonism by nalmefene at opioid receptors. The majority of these adverse events were transient (3–7 days), occurring within 1 day of the first dose, and were mild or moderate in intensity. The authors concluded that as-needed nalmefene was efficacious in reducing alcohol consumption in patients with at least a high drinking risk level at both screening and randomization, and the effect in this subgroup was larger than in the total population. (8)

SENSE was a 12 month study in 675 adults (placebo n=166, nalmefene n=509), mean age 44.3 years, (77% men). 422 of 665 treated patients (63%) completed the study. The reasons for this high drop-out rate are not clear from the paper, which is not fully published. Nalmefene did reduce the number of heavy drinking days and the total alcohol consumption over the study period and at most time points this favoured nalmefene. However, it did not achieve a statistically significant effect when compared to placebo at the primary endpoint of reduction in heavy drinking days and total alcohol consumption at month 6. At month 13 the mean number of heavy drinking days with nalmefene had decreased from 15

to 3 days per month (15 to 6 in the placebo group) and the mean total alcohol consumption from 75g to 16g per day (75g to 27g per day in the placebo group). (4)

In a subgroup post-hoc analysis of the SENSE study, (7) the primary outcome was to evaluate the efficacy and safety of as needed nalmefene 18mg *vs.* placebo in reduction of the monthly number of heavy drinking days and monthly total alcohol consumption at one year in the subgroup of patients with high drinking risk level at both screening and randomisation. A subgroup of 141 of 145 randomised patients on nalmefene and 42 of 42 randomised patients on placebo were analysed. Compared to placebo, total alcohol consumption decreased by approximately 67% in patients receiving nalmefene in this subgroup. The mean number of heavy drinking days decreased from 19 to 5 days per month (19 to 10 with placebo) and the mean total alcohol consumption decreased from 100g to 23.7g per day in the nalmefene group (101 to 47 with placebo) at month 13. At month 13 there was a statistically significant effect of nalmefene compared to placebo in reducing the number of heavy drinking days (-3.6 days/month [95% CI -6.5; -0.7]; p=0.0164) and the total alcohol consumption (-17.3 g/day [95% CI -30.9; -3.8]; p<0.0129). Treatment emergent adverse effects (TEAEs) occurred in 78% of nalmefene patients compared with 62% of patients on placebo. 14% of patients in the nalmefene group dropped out due to TEAEs. None of the patients on placebo dropped out due to TEAEs.

4. Critical evaluation

There were high dropout rates in all three of the phase 3 trials and more patients taking nalmefene withdrew from the studies due to adverse effects. The long term effect (beyond one year) of nalmefene on alcohol consumption has not been studied although there are no limits to the treatment duration specified in the SPC. Whether the drug is taken in the longer term will depend on whether it is being used by the patient to decrease alcohol consumption or establish long term abstinence. In the ESENSE 1 study, the authors discuss the fact that there is no clear-cut answer as to what constitutes a clinically relevant magnitude of reduction of heavy drinking. Various amounts have been suggested and any reduction in alcohol consumption is associated with reduction of morbidity and mortality. In patients who drink more than 10g of alcohol per day, a reduction in alcohol consumption leads to a reduction in the life-time risk of alcohol related death. However the outcomes in the pivotal trials are surrogate endpoints and so longer term benefits associated with nalmefene treatment are unclear. In both ESENSE 1 and 2 there was a large non-specific treatment response, 33% of patients in ESENSE 1 and 18% in ESENSE 2 reducing their drinking prior to starting treatment before any pharmacological intervention. There does not appear to have been any consideration given to what would have happened to these patients, i.e. those who reduce their drinking in the initial 2 week period, in the longer term. There was also a very high placebo response with the average reduction in heavy drinking days of 42% placebo compared with 50% with nalmefene and total alcohol consumption of 50% placebo compared with 61% with nalmefene at 6 months. It could be argued that this is attributable to the ongoing psychosocial support given to both the groups. The licensed indication is based on a post-hoc subgroup analysis; and was not powered for these subgroup analyses. As a results the effect if initial randomisation may have been lost. The clinical trials would have provided a greater level of evidence had this group of patients been chosen originally, or a new, adequately powered, clinical trial been conducted in that subgroup. The study population excluded a large number of patients with other serious co-morbidities, including those with severe hepatic impairment, unstable psychiatric disease or withdrawal symptoms. Co-morbid psychiatric illness is common in people with alcohol dependence. Patients were also excluded if they were taking certain concomitant medication such as insulin, anticoagulants, antianginal agents, systemic steroids, sedatives and hypnotics. Finally there are no active comparator trials (e.g. with naltrexone) and also in order to introduce this drug into clinical practice, the psychosocial support would need to be replicated. It is unclear how this would work with patients who may be receiving different forms and frequencies of psychosocial support. (12)

4.1. Clinical application

One advantage of nalmefene in the treatment of alcohol dependence is that, unlike its comparators, it does not require a goal of abstinence. This may make nalmefene appealing to patients who may otherwise not seek medical treatment for their alcohol dependency. The currently available pharmacological treatment options for alcohol dependence are licensed for a different population of patients; those who require immediate detoxification with a management strategy of abstinence and not reduction of alcohol consumption i.e. patients with moderate/severe alcohol dependency according to NICE CG 115. (9,10) The nalmefene clinical trials did not require immediate detoxification or require a goal of abstinence and therefore might equate to patients with mild alcohol dependence according to NICE guidance. (9,10)

4.2. Safety

The safety profile of nalmefene in patients with at least a high drinking risk level both at screening and randomisation was similar to that observed in the total population. During the 6 month treatment period, approximately 77% of patients taking nalmefene had one or more adverse events (AEs), compared with 67% of patients in the control group. The most commonly reported AEs were dizziness, nausea and insomnia. The AEs with the highest incidences were central nervous system and gastrointestinal events, which had a higher incidence in the nalmefene group than in the placebo group and reflect the antagonism by nalmefene at opioid receptors. The majority of the AEs were transient (3-7 days) occurring within 1 day of the first dose, and were mild or moderate in intensity. During the treatment period, 26 (8%) of patients on placebo and 58 (17.5%) of patients on nalmefene dropped out due to adverse events. (8) Further detail regarding the AEs from the entire clinical study programme is available in the Summary of Product Characteristics. (1)

Hepatic impairment

Nalmefene is contraindicated in patients with severe hepatic impairment (Child-Pugh, group C) because these patients were excluded from the pivotal phase three clinical trials and there is no pharmacokinetic data available in this group. The use of nalmefene in patients with mild or moderate hepatic impairment is cautioned and additional monitoring may be

required. Patients with elevated alanine aminotransferase (ALAT) or aspartate aminotransferase (ASAT) (>3 times ULN) were excluded from the clinical trials, and nalmefene should be used with caution in this group. (1, 10)

4.3. Potential advantages and disadvantages over existing technologies

Nalmefene is taken orally when required. The maximum dose is one tablet per day and should be taken as-needed: on each day the patient perceives a risk of drinking alcohol; one tablet should be taken, preferably 1-2 hours prior to the anticipated time of drinking. If the patient has started drinking alcohol without taking nalmefene, the patient should take one tablet as soon as possible. (1) The level of psychosocial support required with nalmefene is less than required if giving psychosocial intervention on its own and this level of psychosocial support can potentially be given by any healthcare professional. (10) The manufacturer (Lundbeck) is in the process of developing an online psychosocial support tool, which will be free of charge to the NHS. (10) Comparing the clinical and cost effectiveness of nalmefene with naltrexone is difficult as there have been no head-to-head studies comparing these 2 structurally similar opioid antagonists and naltrexone is not licensed for 'when required' use. However, there is a large body evidence to support the use of naltrexone in alcohol dependence which has been shown in 50 RCTs, in 7,793 patients, to reduce the risk of heavy drinking to 83% of the risk in the placebo group, and decreased drinking days by about 4%. (13) There are no routine monitoring requirements for nalmefene unlike naltrexone (1)

4.3.1. Convenience

Because nalmefene is taken orally -and as required, it is convenient for both the patient and the healthcare provider.

4.3.2. Drug cost

Nalmefene costs £3.03 per 18mg tablet, or £42.42 for 14 tablets (approximately 28 days' supply, or £84.84 per 28 days at the maximum dose). (10) Alternatives (although unlicensed for 'when required' use) per 28 days; acamprosate (£28.80) disulfiram (£14), naltrexone (£22.34). (11,14)

4.3.3. Healthcare resource utilisation

Nalmefene could potentially be initiated in primary or secondary care. It may be most appropriate that it is initiated following a full assessment of the patient, by a specialist in alcohol dependence. Nalmefene may be suitable for patients who have previously not sought help for their alcohol dependence.

4.3.4. Suitability for shared care

Nalmefene might be considered suitable for shared care, if the person was stable and deriving benefit, depending on the locally agreed service and the psychosocial support was available.

4.3.5. Likely budgetary impact

Lundbeck have provided a budgetary impact model for nalmefene, summarised below. It is not clear from the data available so far how often and for how long patients will take nalmefene outside the clinical trial setting. As such the model provided is somewhat limited.

Summary of manufacturers budgetary impact model

The price of nalmefene is £3.03 per tablet making the annual prescribing cost an estimated £553, per patient if the drug is taken on an average of 50% of the days (as was the case in the 6 month trials) or £385 if the drug is taken only on 35% of the days, as per the manufacturers model. In a population of 100,000 people (in England), 78,711 will be aged 18 and over. Of these, 6% or 4,644 will have alcohol dependence and there will be 3,901 patients with alcohol dependence who do not need detoxification (i.e. mild dependence). 176 of these are currently treated with psychosocial intervention.
Assuming an uptake of 20%, 35 of these 176 patients will be treated with nalmefene plus psychosocial support. The drug costs per 100,000 population will there be between £13,475 and £19,355 per year depending on how often the drug is taken and assuming an uptake rate of 20%. Annual treatment costs including psychosocial interventions costs are shown below. The model does not include any indication of how many patients are currently receiving naltrexone , and how that would compare in terms of cost.

Annual treatment costs per patient (and per 100,000 population)

Type of treatment	Therapy costs	Drug costs	Total costs
Psychosocial intervention	£1,031 (£36,085)	£0 (£0)	£1,031(£36,085)
Nalmefene (taken on average every other day as per the 6 months trials) plus psychosocial intervention	£613 (£21,455)	£553 (£19,355)	£1,166 (£40,810)
Nalmefene (taken on 35% of days as per the manufacturers model) plus psychosocial intervention	£613 (£21,455)	£385 (£13,475)	£998 (£34,930)

5. Health Economics

The manufacturer of nalmefene has developed a service impact model to consider the likely budgetary impact of introducing nalmefene into the health economy. This model, considers not only the treatment costs, but the overall cost of alcohol dependence including other healthcare costs and societal costs. For NHS England and using the manufacturers assumptions, and a population of 100,000, the net impact of introducing nalmefene is as follows:

- An increase of 8.11% in the number of patients with mild alcohol dependence responding to treatment.
- Assuming nalmefene is taken on 35% of the days, there would be a decrease in the overall treatment costs associated with treating patients with mild alcohol dependence of £1,165 per 100,000 population assuming the existing utilisation of psychosocial support is as described.
- If nalmefene is taken on 50% of the days, there would be an increase in the overall treatment costs associated with treating patients with mild alcohol dependence of £4,725 per 100,000 population assuming the existing utilisation of

psychosocial support is as described.

In addition, the manufacturers have calculated that other alcohol-related healthcare costs would decrease by £13,444, and the impact upon healthcare resource use would be:

- A reduction of 2 inpatient admissions.
- A reduction of 5 outpatient visits.
- A reduction of 10 A&E attendances.

There may be a further reduction in societal costs such as criminal justice system costs and workplace productivity costs. These are clearly much harder to quantify, but the manufacturer has suggested a reduction in societal costs of £44,694.
In London number of admissions with a primary or secondary diagnosis of alcohol is thought to be doubling every six years.

The Scottish Medicines Consortium (SMC) has evaluated the health economic model for NHS Scotland. The detail is not included the detail in this review as the incidence and prevalence of alcohol dependence are very different across the UK; however, in NHS Scotland using a one year time horizon resulted in a cost per QALY of £23,920. The SMC identified a number of limitations with the health economic analysis, the details of which are described in the document. (12)

6. Likely commissioning and funding pathway

Nalmefene is likely to be considered by clinical commissioning groups (CCGs) as part of alcohol or drug and alcohol services. These services are sometimes provided by mental health trusts which would be covered by PBR. CCGs will tender for such services and as a result the funding pathway will depend on who the CCGs have commissioned the service from, and whether this service includes prescribing.

7. Suggested place in therapy

- Nalmefene is the first pharmacological option for the reduction of alcohol consumption in adult patients with alcohol dependence.
- Current drug treatments for alcohol dependence are aimed at a goal of abstinence and generally delivered by specialist alcohol services.
- Nalmefene may be an option for patients that acknowledge they have a problem with alcohol dependence, and want to do something about it.
- The manufacturer anticipates that nalmefene may be initiated in primary care.

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