Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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NHS SCOTLAND

nalmefene 18mg film-coated tablets (Selincro®) SMC No. (917/13)
Lundbeck Limited

06 September 2013

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

ADVICE: following a full submission

nalmefene 18mg film-coated tablets (Selincro®) are accepted for use within NHS Scotland.

Indication under review: 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. Nalmefene should only be prescribed in conjunction with continuous psychosocial support focused on treatment adherence and reducing alcohol consumption. Nalmefene should be initiated only in patients who continue to have a high DRL two weeks after initial assessment.

In a post hoc analysis of two pivotal phase III studies representing the licensed population, nalmefene was shown to significantly reduce alcohol intake compared with placebo, measured as a reduction in heavy drinking days and total alcohol consumption over a six month period.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Published 07 October 2013

Indication

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.

Nalmefene should only be prescribed in conjunction with continuous psychosocial support focused on treatment adherence and reducing alcohol consumption.

Nalmefene should be initiated only in patients who continue to have a high DRL two weeks after initial assessment.

Dosing Information

At the initial visit, the patient's clinical status, alcohol dependence and level of alcohol consumption (based on patient reporting) should be evaluated. Thereafter, the patient should be asked to record his or her alcohol consumption for approximately 2 weeks. At the next visit, nalmefene may be initiated in patients who continue to have a high DRL over this 2-week period, in conjunction with psychosocial intervention focused on treatment adherence and reducing alcohol consumption.

Nalmefene is to be taken as-needed: one tablet on each day the patient perceives a risk of drinking alcohol, preferably 1 to 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. The maximum dose is one tablet per day. Nalmefene can be taken with or without food.

Product availability date

7 May 2013

Summary of evidence on comparative efficacy

Nalmefene is an opioid system modulator with antagonistic activity at the μ- and δ-opioid receptors and partial agonist activity at the κ-opioid receptors. Acute alcohol intake results in mesolimbic dopamine release which can provide positive reinforcement. Nalmefene is thought to counteract the positive reinforcement effects and to reduce alcohol consumption, possibly by modulating these cortico-mesolimbic functions.[1] It is the first medicine to be licensed for the reduction of alcohol consumption in alcohol dependent patients. Current management of harmful drinkers with mild alcohol dependence is primarily based on a non-pharmacological approach using psychological approaches such as Alcohol Brief Interventions. Other medicines (acamprosate, naltrexone and disulfiram) are licensed for maintaining abstinence following alcohol withdrawal.

The evidence to support the use of nalmefene comes from the results of two identical 24-week phase III European studies (ESENSE 1 and 2) and one 52-week phase III safety and efficacy study (SENSE).[2,3,4]

The ESENSE 1 and 2 studies included a 1 to 2 week screening period, a 24-week double-blind treatment period, a 4-week double-blind run-out period and a 4-week safety follow-up.[2,3] Eligible patients were aged ≥18 years, with a diagnosis of alcohol dependence according to Diagnostic and Statistical Manual of Mental Disorders 4th edition text revision (DSM-IV-TR); ≥6 heavy drinking days (HDD: defined as a day with alcohol ≥60g/day for men and ≥40g/day for women) and ≤14 consecutive abstinent days in the 4 weeks before screening; and an average alcohol consumption of ≥medium drinking risk level (DRL) (i.e. alcohol ≥40g/day for men and ≥20g/day for women). (Note: one UK unit = 8g alcohol).

Patients were randomised in a ratio of 1:1 to receive 24-weeks of treatment with nalmefene 18mg or placebo. Study medication was taken as-needed with one tablet taken on each day the patient perceived a risk of drinking alcohol, ideally 1 to 2 hours before anticipated time of drinking. Patients recorded each date on which study medication was taken. All patients took part in a psychosocial programme (BRENDA), a motivational and adherence-enhancing intervention which was provided at weeks 0, 1, 2, and then monthly. At 24 weeks, the patients randomised to nalmefene were re-randomised in a ratio of 1:1 to receive nalmefene (18mg as-needed) or placebo for the 4-week run-out period but limited data are available from this.[1]

There were two co-primary outcomes: the change from baseline to 6 months in number of monthly HDDs and the change from baseline to 6 months in total alcohol consumption (mean daily alcohol in g/day over one month). Patients self-reported their daily alcohol consumption using the timeline follow-back method to estimate retrospectively the number of standard drinks each day (defined as a 24-hour period starting at 6am to 6am the following morning). All efficacy analyses were conducted in the full analysis set (FAS) using a mixed model repeated measures (MMRM) methodology which used all the available monthly data over the 6-month treatment period.

Between screening and randomisation, a proportion of patients in the FAS reduced their drinking to <6 HDDs or <medium DRL: 18% (102/579) in ESENSE 1 and 33% (218/655) in ESENSE 2, no longer within the pre-specified inclusion criteria. To address this issue, post hoc analyses were performed in the subgroup of patients who had a high or very high DRL at both screening and randomisation (i.e. the licensed population).[1] This comprised 58% of the total ESENSE 1 population and 46% of the total ESENSE 2 population.

Results of the post hoc MMRM analyses in the licensed population found that there were significantly greater reductions in HDDs and total alcohol consumption in patients treated with nalmefene than with placebo. The treatment difference in the change from baseline to 6 months in HDD was -3.7 days/month (95% confidence interval [CI]: -5.9 to -1.5), p=0.0010 in ESENSE 1 and -2.7 days/month (95% CI: -5.0 to -0.3), p=0.0253 in ESENSE 2. The treatment difference in the change from baseline to 6 months in total alcohol consumption was -18.3g/day (95% CI: -26.9 to -9.7), p<0.0001 in ESENSE 1 and -10.3 g/day (95% CI: -20.2 to -0.5), p=0.0404 in ESENSE 2.[1-5]

There was a high level of discontinuation in both licensed populations: in ESENSE 1, 50% and 32%, and in ESENSE 2, 30% and 28%, in the nalmefene and placebo groups, respectively. Sensitivity analyses assessed the treatment effect of the co-primary outcomes when missing data was handled using different imputation methodologies. This found some inconsistencies in whether statistical significance was achieved or not and uncertainty as to the magnitude of benefit.[1] A further analysis was carried out in 'completers' of the licensed population in which all withdrawals were treated as non-responders. This found, in ESENSE 1, that HDDs in the nalmefene group reduced from baseline of 23 days/month (n=171) to 9 days/month at 6 months

(n=85), and in the placebo group, from 23 days/month (n=167) to 14 days/month (n=114) respectively. In ESENSE 2, HDDs in the nalmefene group reduced from baseline of 23 days/month (n=148) to 10 days/month at 6 months (n=103), and in the placebo group from 22 days/month (n=155) to 12 days/month (n=111) respectively. In ESENSE 1, total alcohol consumption in the nalmefene group reduced from baseline of 102g/day (n=171) to 40g/day at 6 months (n=85), and in the placebo group from 99g/day (n=167) to 57g/day (n=114) respectively. In ESENSE 2, total alcohol consumption in the nalmefene group reduced from baseline of 113g/day (n=148) to 44g/day at 6 months (n=103) and in the placebo group from 108g/day (n=155) to 52g/day (n=111) respectively.[1]

The key secondary outcome was DRL level response at 6 months, which was defined as downward shift from very high DRL at baseline to ≤medium DRL at 6 months, or from high or medium DRL at baseline to ≤low DRL at 6 months. Post hoc analyses in the licensed populations reported responses of 61% in the nalmefene group versus 43% in the placebo group in ESENSE 1 (p=0.0006), and 52% versus 41% respectively in ESENSE 2 (p=0.062).[4,5]

Results for Clinical Global Impression-Improvement (CGI-I: a 7-point scale assessed by the clinician with 1=very much improved to 7=very much worse) and Clinical Global Impression-Severity (CGI-S: a 7-point scale with 1=normal to 7=most extremely ill) showed that nalmefene was significantly superior to placebo in the licensed populations of ESENSE 1 and 2. In ESENSE 1 and 2, there were significantly greater reductions with nalmefene versus placebo in alanine aminotransferase and gamma glutamyltransferase levels at 6 months in the licensed populations.[1,2,3,4,5]

Quality of life assessments, using the SF-36 mental and physical component scores, EuroQol (EQ-5D) utility index and health state scores and the Drinker Inventory of consequences (DrInc-2R) total score, showed significantly greater improvements with nalmefene versus placebo in pooled analysis of the licensed subgroups of ESENSE 1 and 2.[6]

A similar phase III study (SENSE) assessed longer-term (one year) efficacy as a secondary outcome in patients with alcohol dependence. In the licensed population (28% [187/675] of the total population) of SENSE, nalmefene significantly reduced HDDs and total alcohol consumption versus placebo at 12 months.[1,7,8]

Summary of evidence on comparative safety

Pooled safety analyses were performed in the alcohol dependence pool which comprised the three studies (ESENSE 1 and 2 and SENSE).[1] Treatment emergent adverse events were reported in 75% (855/1144) nalmefene and 63% (500/797) placebo patients of the total population. In the subgroup of patients with high or very high DRL (licensed population), treatment emergent adverse events were reported in 75% and 62% of patients respectively, suggesting the incidence was not dependent on baseline DRL.

Dizziness, nausea and insomnia/sleep disorders were reported in approximately three to four times more nalmefene than placebo treated patients. Dizziness and nausea were more frequent during the first month (16% and 18% respectively) and then reduced to 1 to 2% per month. Insomnia was reported in 13% of nalmefene and 5.4% of placebo patients. Day- or night-time sleep disorders were reported in 29% of nalmefene treated patients. Psychiatric

disorders including confusion, abnormal thinking and hallucinations were reported in 2.9% of nalmefene patients, approximately three times more frequent than placebo patients.[1]

In the pooled safety analysis, the withdrawal rate was high (43% in the nalmefene group and 34% in the placebo group). The most common reason for withdrawal was withdrawal of consent (16% versus 13% respectively). Withdrawal due to adverse events was reported in 11% and 3.8% of patients respectively.[1] However, since adverse events were not set as a primary reason for discontinuation, this may be an underestimate.[1]

Summary of clinical effectiveness issues

The company submission provides evidence from three phase III studies which found that nalmefene was superior to placebo in reducing alcohol intake measured by the number of HDDs and total alcohol consumption.

The main evidence supporting the licensed indication comes from post hoc analyses of the ESENSE 1 and 2 studies. There was a high proportion of patients in the FAS of each study who considerably reduced their alcohol consumption during the 1 to 2 weeks between screening and randomisation to such a degree that there was little additional margin for further reduction. Because of this, post hoc analyses were performed in the subgroups of patients who still had a high or very high DRL at baseline (58% and 46% of the total ESENSE 1 and 2 populations, respectively). The studies were not powered for these subgroup analyses and the effect of initial randomisation may have been lost.

Another limitation of the evidence was the high drop out rates in all three studies, with rates higher in nalmefene than placebo treated patients. Whilst high, the drop out rates were comparable to those reported in other recent placebo-controlled studies conducted in patients with alcohol dependence. In ESENSE 1 and 2, approximately half of the total nalmefene population discontinued treatment, while in SENSE, 39% discontinued. Various sensitivity analyses were performed to account for missing data and to test the robustness of the primary results. In the total study and licensed populations, there were some inconsistencies across the sensitivity analyses and the EMA described a degree of uncertainty about the exact magnitude of the beneficial effect. To avoid the issue of which was the most appropriate analysis, a further analysis was conducted in 'completers' with all withdrawals treated as non-responders. These results are similar to those using the pre-specified MMRM analysis and are reported in the Summary of Product Characteristics.

The ESENSE 1 and 2 studies excluded patients with co-morbid psychiatric conditions and SENSE excluded patients with severe psychiatric conditions. Since co-morbid psychiatric illness is common in people with alcohol dependence, it is unclear how well the study results can be extrapolated to patients with mental health issues. In the pivotal studies, there was an extensive list of disallowed concomitant medications which included insulin, anticoagulants, antianginal agents, systemic steroids, sedatives and hypnotics.

All study patients received psychosocial support in the form of BRENDA at each study visit. It is unclear how well the study results can be extrapolated to patients who receive different forms or frequencies of psychological support.

Patients self-reported their alcohol consumption which has limitations due to its subjectiveness.

Controlled clinical data on the use of nalmefene are limited to one year and caution is advised if nalmefene is prescribed for more than one year.

The outcomes measured in the pivotal studies are surrogate endpoints therefore longer term benefits associated with nalmefene treatment are unclear. However, the company presented analyses of expected harm reduction in terms of alcohol-related physical health outcomes, injuries and social consequences from both modelling and literature data. These indicate that even a moderate decrease in drinking level may be associated with a decrease in both harmful events and in the relative risk of medical issues linked to excessive alcohol.

Nalmefene offers a licensed treatment option in conjunction with psychosocial support for patients with alcohol dependence who have a high drinking level whose goal of treatment is to reduce alcohol consumption. However, there is no consensus over whether this should be an option or whether the goal should be abstinence. Nalmefene is recommended to be taken as-needed with one tablet on each day the patient perceives a risk of drinking alcohol, preferably 1 to 2 hours prior to the anticipated time of drinking. This dosing allows the patient to take control of their management but also requires a willingness to comply and anticipate drinking risk appropriately. During the studies, nalmefene treatment was recorded as taken on 48% to 57% of days in the total populations.[2,3]

It is expected, although not entirely established, that this new licensed medicine aiming for reduction of alcohol intake rather than for abstinence will be prescribed more commonly in primary than secondary care in Scottish clinical practice. Responses from experts contacted by SMC suggest that the way this medicine will be managed in practice still needs some deliberation. There is likely to be service implications associated with the provision of psychosocial support. There is also the potential for different models of care.

Summary of comparative health economic evidence

The company submitted a cost-utility analysis over a five year time horizon comparing nalmefene plus psychosocial intervention with psychosocial intervention alone. A Markov model was used which consisted of a short-term phase (1 year) followed by a longer term phase (years 2-5). The short-term phase of the model captured treatment efficacy and the incidence of alcohol-related harmful events and deaths. The cycle length for this period was one month to reflect the data time points in the studies. In the first year of the model, patients were in one of five WHO-defined alcohol consumption health states: very high risk, high risk, medium risk, low risk and abstinence. Patients started the model in either the very high risk or high risk health states based on the proportion at randomisation in the studies. After each cycle, patients could then move among the five drinking risk levels at treatment-specific rates for the first year of the model.

The longer-term phase modelled the maintenance of effect of treatment, patient progression, and the incidence of alcohol-related harmful events and deaths. A one-year cycle length was applied. At the start of the longer-term model patients were categorised into three health states: controlled drinking, medium-risk drinking, and high/very high risk drinking. Patients who had achieved controlled drinking after one year of nalmefene were assumed to discontinue treatment. Patients in the medium-risk health state at one year were assumed to continue on treatment, but this only applied to around 10% of patients in the model. In the high/very high

risk drinking health state, patients moved to second-line treatment which involved assisted alcohol withdrawal followed by naltrexone or acamprosate plus psychological treatment.

The clinical data used in the first year of the model were taken from a pooled analysis of the ESENSE 1, ESENSE 2 and SENSE studies. The pooled data were then used to derive monthly transition probabilities between the five drinking risk level health states. The transition probabilities were based on the count of patients each month in each WHO health state from the pooled studies. Beyond one year, a relapse rate of 19% was applied to patients in the controlled drinking health state. For patients who progressed to second-line treatment, a relapse rate of 82% was applied based on the relevant NICE clinical guideline meta-analysis of patients who had received assisted alcohol withdrawal and treatment with acamprosate or oral naltrexone. The effects of alcohol-attributable harmful events by drinking risk levels were included in the model in two categories: immediate-drinking events (transport injuries, other injuries, ischemic stroke and ischemic heart disease) and continuous-drinking events (liver cirrhosis, pancreatitis, lower respiratory infections, and haemorrhagic stroke).

The utility values were derived from EQ-5D data collected in the nalmefene studies at baseline, week 12, week 24, week 36 and week 52. In the short-term phase, the company used an area under the curve approach to estimate the quality-adjusted life-year (QALY) gain from treatment. Then, in the longer term phase, the EQ-5D estimates from the studies were pooled to give values for the three health states.

Resource use included drug costs, psychosocial intervention and treatment of alcohol-attributable adverse events. Psychosocial intervention was assumed to be delivered on a monthly basis during a usual medical consultation, with 75% of patients receiving this in primary care (standard GP visit) and 25% at the specialist care level (drug and alcohol services).

In the base case analysis (five year time horizon), the submitting company estimated that nalmefene plus psychosocial intervention was the dominant treatment, with estimated savings of £394 and a QALY gain of 0.0722. The probabilistic sensitivity analysis indicated there was 99.68% probability nalmefene is cost-effective at £20k per QALY and 99.74% probability at £30k per QALY. Using a one year time horizon resulted in a cost per QALY of £23,920.

The following limitations were noted:

- There was some concern at NDC that the assumptions made about the costs of delivery of nalmefene treatment in practice may have been underestimated. Sensitivity analysis showed the results were relatively sensitive to the number of medical visits included in the model. The company also provided additional sensitivity analysis to further test this aspect of the model by assuming a higher proportion of nalmefene-treated patients would receive care at a specialist level rather than in primary care. The results indicated that nalmefene remained dominant even if 75% of treatment was delivered in specialist level services. If all nalmefene treatment was delivered in specialist level services, the cost per QALY was £1,232.
- The cost of nalmefene was estimated using an observed case approach taken from the pooled analysis where treatment was estimated to be used 35% of days in one year. Sensitivity analysis showed the cost per QALY increased to £291 when nalmefene was assumed to be taken on a daily basis.
- The relapse rate applied in the model appears low in comparison with the relapse rate estimated in the relevant NICE clinical guideline meta-analysis. While the patients in the NICE guideline are more severe and are therefore more likely to relapse, the difference in

the relapse rates may not be appropriate. However, the company argued that the different relapse rates were justified as they applied to different groups of patients and, in addition, the relapse rate was not a key driver of the model.
- A different method was used to apply the utility values in first year compared with the rest of the model. Additional sensitivity analysis was provided which showed no bias was introduced by the base case approach.

Given the robustness of the cost-effectiveness result to changes to adjust for the weaknesses in the analysis, the economic case was considered to be demonstrated.

Summary of patient and public involvement

Patient Interest Groups Submissions were received from:
- British Liver Trust
- Action on Pain

Additional information: guidelines and protocols

The National Institute for Health and Care Excellence (NICE) published clinical guideline 115 "Alcohol-use disorders: diagnosis, assessment and management of harmful drinking and alcohol dependence" in February 2011.[9] This recommends that for people with mild dependence (SADQ score ≤15), without significant co-morbidity, who have adequate social support, a treatment goal of a moderate level of drinking should be considered unless the person prefers abstinence or there are other reasons for advising abstinence. People with moderate dependence (SADQ score 15 to 30) usually need assisted alcohol withdrawal typically in the community setting and those with severe dependence (SADQ of >30) need assisted alcohol withdrawal typically in an in-patient or residential setting. Abstinence is considered the appropriate goal for most people with alcohol dependence and people who misuse alcohol and have significant psychiatric or physical co-morbidity. For those who prefer a goal of moderation but from whom there are considerable risks, abstinence should be strongly advised, but treatment should not be refused.

Recommended treatment for harmful drinkers with mild alcohol dependence is psychological intervention focused specifically on alcohol-related cognitions, behaviour problems and social networks. For those who have not responded to psychological interventions alone, or who have specifically requested a pharmacological intervention, acamprosate or naltrexone in combination with psychological intervention can be considered. For people with moderate and severe alcohol dependence, assisted withdrawal is recommended including benzodiazepine therapy. Recommended treatments after successful withdrawal for people with moderate to severe alcohol dependence include acamprosate and naltrexone in combination with an individual psychological intervention. Disulfiram, in combination with an individual psychological intervention, is an alternative for people unsuitable for acamprosate and naltrexone and for people who prefer disulfiram but understand its relative risks.

The British Association for Psychopharmacology published "evidence-based guidelines for the pharmacological management of substance abuse, harmful use, addiction and co-morbidity: recommendations from BAP" in 2012. [10] This guideline includes recommendations for the

management of alcohol withdrawal and detoxification and for preventing relapse and maintaining abstinence. The guideline recommends that:

- acamprosate can be used to improve abstinence rates.
- naltrexone can be used to reduce the risk of a lapse becoming a relapse but there is less evidence to support its use in maintaining abstinence.
- for acamprosate and naltrexone there is no consistent evidence to suggest which types of patient will respond and relapse prevention medication should be offered to/considered for everyone who is alcohol dependent wanting to be abstinent.
- disulfiram is effective if intake is witnessed. It can be offered as a treatment option for patients who intend to maintain abstinence and for whom there are no contra-indications.
- baclofen should be considered if a patient wants to be abstinent, has high levels of anxiety and has not benefited from or is unable to take acamprosate, naltrexone or disulfiram.

The Scottish Intercollegiate Guidelines Network (SIGN) published guideline 74 "The management of harmful drinking and alcohol dependence in primary care" in September 2003 (updated 2004).[11] This guideline is limited by its age but recommends acamprosate in newly detoxified dependent patients as an adjunct to psychosocial interventions. Supervised oral disilfiram may be used to prevent relapse but patients must be informed that this is a treatment requiring complete abstinence and be clear about the dangers of taking alcohol with it.

These guidelines predate the availability of nalmefene.

Additional information: comparators

No other medicines are specifically licensed for reducing alcohol consumption. Other medicines, acamprosate, naltrexone and disulfiram are licensed for maintenance of abstinence after alcohol withdrawal.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Nalmefene	**18mg on each day the patient perceives a risk of drinking alcohol**	**551***

Costs from eMIMs on 20 June 2013. * nalmefene costs £3.03 per 18mg tablet. The cost above is based on the assumption that nalmefene is used on 50% of days within one year as indicated in the total populations of the clinical studies.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 90,781 in year 1 and 92,789 in year 5 based on a prevalence rate of 8%. The estimated uptake rate was 2% in year 1 and 8.4% in year 5. The company included a discontinuation rate of 17.50% in all 5 years. The gross impact on the medicines budget was estimated to be £576k in year 1 and £2.474m in year 5. No medicines were assumed to be displaced.

The company also submitted a budget impact template showing another scenario using a lower prevalence of 4.9%. The submitting company estimated the population eligible for treatment to be 55,603 in year 1 and 56,834 in year 5. The company included a discontinuation rate of 17.50% in all 5 years. The gross impact on the medicines budget was estimated to be £353k in year 1 and £1.516m in year 5.

Given the Scottish Government priority to reduce alcohol misuse, uptake rates of treatment could be considerably higher.

It should also be noted that the introduction of nalmefene is likely be associated with service implications to provide psychosocial support.

References

The undernoted references were supplied with the submission. The one shaded grey is additional to those supplied with the submission.

1. European Medicines Agency European Public Assessment Report (EPAR) for Selincro® EMEA/H/C/002583/0000 www.ema.europa.eu [accessed 4 June 2013]

2. Mann K, Bladstrom A, Torup L et al. Extending the Treatment Options in Alcohol Dependence: A Randomized Controlled Study of As-Needed Nalmefene. Biol Psychiatry 2013;73:706-713.

3. Gual A, He Y, Torup L et al. A randomised, double-blind, placebo-controlled, efficacy study of nalmefene, as-needed use, in patients with alcohol dependence. European Neuropsychopharmacology 2013 DOI.org/10.1016/j.euroneuro.2013.02.006

4. van den Brink W, Aubin H-J, Bladström A et al. ESENSE 1 - randomised controlled 6-month study of as-needed nalmefene: subgroup analysis of alcohol dependent patients with high drinking risk level. Presented at the 21st European Congress of Psychiatry Nice, France, 6-9 April 2013.

5. van den Brink W, Aubin H-J, Sorensen P et al. ESENSE 2 - randomised controlled 6-month study of as-needed nalmefene: subgroup analysis of alcohol dependent patients with high drinking risk level. Presented at the 21st European Congress of Psychiatry Nice, France, 6-9 April 2013.

6. Francois C, Rahhali N, Chalem Y et al. Consequences of the reduction of alcohol consumption on patient's reported outcomes with the use of nalmefene. Presented at ISPOR 18th Annual International Meeting New Orleans, LA, USA, May 18-22, 2013.

7. van den BW, Sorensen P, Torup L et al. Long-term efficacy, tolerability, and safety of nalmefene as-needed in alcohol-dependence: a randomised, double-blind, placebo-controlled study. Presented at 35th Annual RSA Scientific Meeting San Francisco, California, USA, 23-27 June, 2012.

8. van den BW, Sorensen P, Torup L et al. Long-term efficacy of nalmefene as-needed in alcohol dependent patients with high drinking risk levels: results of a subgroup analysis. Presented at 21st European Congress of Psychiatry, Nice, France, 6-9 April 2013.

9. National Institute for Health and Care Excellence (NICE). Clinical guideline 115. Alcohol use disorders: diagnosis, assessment and management of harmful drinking and alcohol dependence, February 2011. www.nice.org

10. Ling-ford Hughes AR, Welch S, Nutt DJ. BAP updated guidelines: evidence-based guidelines for the pharmacological management of substance abuse, harmful use, addiction and co-morbidity: recommendations from BAP. J Psychopharmacology 2012. DOI: 10.1177/0269881112444324

11. Scottish Intercollegiate Guidelines Network (SIGN). Guideline 74: The Management of Harmful Drinking and Alcohol Dependence in Primary Care, September 2003. www.sign.ac.uk

This assessment is based on data submitted by the applicant company up to and including 16 August 2013.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.