NICE National Institute for Health and Care Excellence

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Single Technology Appraisal (STA)

Nalmefene for the reduction of alcohol consumption in people with alcohol dependence [ID660]

Dear [redacted]

The Evidence Review Group, School of Health and Related Research, University of Sheffield, and the technical team at NICE have now had an opportunity to take a look at the submission received on the 28th February by Lundbeck Limited. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **5pm** on **Friday 04 April 2014**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be emailed to us separately as attachments or sent on a CD.

If you have any further queries on the technical issues raised in this letter then please contact Caroline Hall, Technical Lead caroline.hall@nice.org.uk. Any procedural questions should be addressed to Donna Barnes, Administrator (donna.barnes@nice.org.uk) in the first instance.

Yours sincerely

Helen Knight
Associate Director – Appraisals

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Centre for Health Technology Evaluation

Encl. checklist for in confidence information

Literature searching

- Please provide justification (including limitations) for restricting the literature searches to English language studies only.

Section A: Clarification on the treatment pathway

A1. **Priority Question:** Please clarify why the economic model does not take into account the recommendations in NICE clinical guideline 115 (see points a-c below). Please provide an indicative incremental cost-effectiveness ratio where nalmefene is used only in those patients who did not respond to psychological interventions as recommended in the NICE clinical guideline.

a. The 'general principles for all interventions' section of the NICE clinical guideline 115 states that 'all interventions for people who misuse alcohol should be delivered by appropriately trained and competent staff.'

b. In section 1.3.3 of the NICE clinical guideline 115 it is stated that acamprosate or naltrexone can be prescribed for those that have not responded to a psychological intervention alone, or those that have specifically requested a pharmacological intervention.

c. Section 1.3.3 of the NICE clinical guideline 115 also relates to delivering psychological interventions. This states that therapies should usually consist of one 60-minute session per week for 12 weeks.

A2. **Priority Question:** Please clarify whether the clinicians whose advice was used to assume 12 months of pharmacological intervention or psychosocial intervention + nalmefene before considering naltrexone were based in England. The ERG's clinical advisers indicate that people would not be allowed to remain in the very high or high drinking risks for this length of period before naltrexone was used. They suggest 3 months is more likely. Please clarify the likely impact of this assumption on the cost-effectiveness ratio.

A3. **Priority Question:** The ERG's clinical advisers also indicate that maintaining patients on nalmefene beyond 12 months may be unlikely in those reduced to moderate risk levels. Additionally the Summary of Product Characteristics also states that '*Caution is advised if Selincro is prescribed for more than 1 year'.* Please clarify the implication of altering this assumption on the incremental cost-effectiveness ratio.

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A4. Please provide details on potential complications of individuals taking nalmefene with other opiates. For example, the use of over the counter medicines such as cough medicine that contain codeine, or the use of opiates in the in the event of an accident.

Section B: Clarification on the effectiveness data

B1. Please clarify if study selection, data extraction and quality assesment were undertaken independently by a minimum of two reviewers for each of the three systematic reviews (pharmacological interventions, psychosocial interventions and cost-effectiveness). If not, please explain why.

B2. Please provide a detailed breakdown of all excluded full text studies (that is, full reason for exclusion and reference) for the systematic reviews of nalmefene and naltrexone.

B3. Please provide further details (for example, number of patients with alcohol dependency, length of abstinence prior to randomisation, efficacy [baseline, final, difference and safety results], if relevant) on the following nalmefene studies in the European Public Assessment Report by each treatment arm which were excluded from the submission to NICE: CPH-101-801 (Karhuvaara et al), CPH-101-701 (unpublished) and CPH-101-299 (Anton et al., 2004). In addition, the Karhuvaara et al. study included a a large group of heavy drinkers (93%) that met the criteria for alcohol dependence. Please clarify why evidence from this (or other similar) studies would not be useful given the majority of alcohol dependent people.

B4. Please provide the evidence source for the following statement in Table B8 (page 78; final column): 'the TFLB method…has been widely used in clinical studies and has been shown to give reliable retrospective self-reports of drinking in outpatients'.

B5. Please provide the reasons for withdrawal for patients that were randomised but not treated in ESENSE1 (Figure B4; page 88), ESENSE2 (Figure B5; page 89) and SENSE trials (Figure B6; page 90).

B6. Please provide tabulated outcome data for all outcomes (including sample size) for each treatment arm of the ESENSE1, ESENSE2 and SENSE trials as baseline (±SD), final (±SD), mean difference from placebo, 95% confidence intervals and p values for continuous outcomes or by event rates, odds ratios, 95% confidence intervals and p values for binary data.

B7. Please clarify why a meta-analysis of the safety and efficacy evidence using individual patient level data or aggregate data for all outcomes of interest was not undertaken. A pooled analysis primarily focuses on treatment groups rather than on studies and this approach does not consider the validity of the comparisons; thus it is subject to confusion bias (also known as Simpson's paradox).

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B8. The baseline characteristics of people within ESENSE1 and ESENSE2 differed (Table 10-8; page 287), as did the effect size of nalmefene. Please clarify whether any analysis was undertaken to determine if any of the characteristics were treatment effect modifiers.

B9. Please clarify whether any factors were considered as random in the mixed model repeated measures analysis and what interaction terms were investigated.

B10. Please clarify why the pooled effects analysis did not consider weighting for within and between study variability.

B11. Please clarify the specific assumptions that are being made when evaluating the different methods of imputation of missing data. Please explain why the mixed model results are assumed to be valid when they are said to be based on “patients adhering to treatment” (page140).

B12. The results of the multiple imputation approach give more consistent results between ESENSE1 and ESENSE2 and are more conservative; please explain why these results should not be considered as the base case.

B13. Please clarify what is meant by observed cases in tables such as Table B46 (page 156).

B14. Please clarify whether the studies in Table B10 (page 91) were full intention to treat analyses, or whether these were modified intention to treat analyses.

B15. Please provide further details (methodology, sample size and tabulated results) on the survey conducted by Lundbeck on the use of psychosocial interventions in England (page108).

B16. Please provide further information (or justification) for not undertaking the methodological quality assessment of included studies in the systematic review of naltrexone and psychosocial interventions.

B17. Please clarify if any attempt was made to seek clarification (including obtaining relevant data that was not reported in the published papers) from the authors of the included naltrexone and psychosocial intervention studies (Table B29; page 124).

B18. Please clarify the methods of data synthesis in the systematic review of naltrexone and psychosocial interventions. In addition, please explain why the outcome data from the psychosocial intervention trials were not amenable to meta-analysis.

B19. Please provide safety outcome, compliance and adherence data (including sample size) for each treatment arm of the ESENSE1, ESENSE2 and SENSE trials separately for the licensed population and the total population.

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Section C: Clarification on cost-effectiveness data

C1. Please clarify whether the risks of serious events in the model are adjusted for mortality. For example, the probability of moving from very high risk on treatment to heart disease is 0.14% for males in the 1st year (cell i196 of Input summary General) whilst mortality risk is 0.03% (cell i276). Does that imply that overall risk was 0.17%, or should the non-fatal risk be 0.11%?

C2. Please clarify whether there is an error in the model regarding mortality rates from people progressing from initial serious event. For example cell AK72 in the Markov Nalmefene sheet formula currently reads

"=AJ71+AK71*(1-VLOOKUP(ISG!$O$17,'GP Mortality'!$F$38:$I$120,4,FALSE))"
whereas we suspect it should read
"=(AJ71+AK71)*(1-VLOOKUP(ISG!$O$17,'GP Mortality'!$F$38:$I$120,4,FALSE))

If this formula is incorrect, please amend the model where required to ensure internal validity.

C3. Please clarify why a half-cycle correction has not been undertaken.

C4. Please clarify why utilities for serious events are assumed invariant of time.

C5. Please clarify why the very high risk utility is used for the very high/high risk group and the abstinence utility for the low/abstinent group. Please also clarify the impact on the results where the alternative assumption is used.

C6. Please clarify how drop-outs were handled within the utility calculations.

C7. Please clarify whether having a non-fatal serious event (such as heart disease) is associated with mortality risk. Cell G102 on the 'Data Store' Sheet implies no mortality.

C8. Please clarify why mortality rates associated with chronic events are diminished by underlying general population mortality. For example, cell AT71 in the Markov Nalmefene sheet, the risks of mortality from events are multiplied by the survival rate. It is expected that the risks reported are not conditional on survival. If this is an error further amendments would be needed to maintain internal validity.

C9. Please clarify why it is assumed that the summed probability of non-fatal lower respiratory infections, transport injuries and other injuries are not assumed mutually exclusive from the summed totals of heart disease, ischaemic stroke, haemorrhagic stroke, liver cirrhosis and pancreatitis and fatal lower respiratory infections, transport injuries and other injuries, yet non-fatal heart disease, ischaemic stroke, haemorrhagic stroke, liver cirrhosis and pancreatitis is assumed mutually exclusive

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from fatal heart disease, ischaemic stroke, haemorrhagic stroke, liver cirrhosis and pancreatic lower respiratory infections, transport injuries and other injuries events.

Section D: Textual clarifications and additional points

D1. Please confirm whether the data are correct in Figure B4 (page 89) for the nalmefene + PI group (for example the number of withdrawals plus the number of patients who completed the study does not equate to the number of patients treated).

D2. Please clarify and explain the apparent discrepancies between the manufacturer's submission (Table B13; page 95) and the Summary of Product Characteristics (Table 2) with respect to the TAC R70 (≥ 70% reduction in total alcohol consumption) value.

D3. Please comment on a rapid response published in the BMJ by Alain Braillon (available at http://www.bmj.com/content/348/bmj.g1531?tab=responses) which states that "in 1998 Contral Pharma Ltd tried to develop nalmefene for alcohol related problems but in 2003 nalmefene didn't succeed to meet phase III clinical end points statistically significantly. These data must be disclosed too". If appropriate, and available please provide the relevant data from this trial, or state the reason for not doing so.