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29th July 2014

Dear Donna

Single Technology Appraisal - Nalmefene for reducing alcohol consumption in people with alcohol dependence [ID660]
Manufacturer's response to the Appraisal Consultation Document

Thank you for the opportunity to comment on the Appraisal Consultation Document. Our comments are set out in the table overleaf.

We have endeavoured to address the specific topics on which the Committee sought comments and would particularly like to draw the Committee's attention to our views on whether or not the usual 3-month implementation period should be extended in the case of this appraisal (section 5.1 of the ACD). We do not believe that any extension of the normal time period is either necessary or appropriate in this case and have given the reasons for our view in the table.

We look forward to receiving the Final Appraisal Determination in due course.

Yours sincerely

[redacted]

[redacted]

[redacted]

Nalmefene for alcohol dependence ID660
Response to the Appraisal Consultation Document from Lundbeck Limited

Page	Section	Text	Comments
-	General	-	Lundbeck Limited ("we") would like to thank the Appraisal Committee for the opportunity to comment on the Appraisal Consultation Document (ACD) for nalmefene. To the best of our knowledge, we believe that the Appraisal Committee has taken all relevant evidence into account. We confirm that the summaries of clinical and cost-effectiveness are reasonable interpretations of the evidence and believe that the provisional recommendations form a sound and suitable basis for guidance to the NHS.
4	Section 2.1	"…adult patients with alcohol dependence who have a **high drinking risk level** without physical withdrawal symptoms and who do not require immediate detoxification'."	We would also propose that the equivalent units of alcohol are added for clarification: 7.5 units or more a day for a man and 5 units or more a day for a woman.
4	Section 2.1	"Nalmefene is administered orally as 18mg film-coated tablets. The maximum dose is 1 tablet per day.	Please amend this paragraph to read: "Nalmefene is administered orally as 18mg film-coated tablets **and taken each day that the patient is at risk of drinking alcohol.** The maximum dose is 1 tablet per day."
5	Section 3.2	"Psychosocial intervention (in the form of BRENDA) was provided to all treatment groups in the 3 studies."	We think it would be helpful for commissioners and prescribers to clarify here that BRENDA is a non-disease specific approach which focuses on enhancing motivation, behavioural change and adherence to treatment.
6	Section 3.3	"A heavy drinking day was defined as alcohol consumption of 60 g/day or more (equivalent to 7.5 units or more) for men and 40 g/day or more (equivalent to 5 units or more) for women."	We believe it is important to clarify that the heavy drinking day (HDD) thresholds used in the clinical trials are in accordance with the WHO classification of drinking risk levels.
6	Section 3.4	"…Patients were then instructed to take 1 tablet (the maximum daily dose)…	Please amend this sentence to read "…Patients were then instructed to take 1 tablet (the maximum daily dose) **on an as-needed basis**…
8	Section 3.9	"The treatment difference in the changes from baseline to 6 months in the number of heavy drinking days was −3.7 days per month (95% confidence interval [CI] −5.9 to −1.5, p=001) in ESENSE1…"	There is a typographical error in the p-value; the correct value is p=0.001.
12	Section 3.16	"The 1-year cycle aimed to take account of treatment efficacy and patient adherence…"	Please correct this sentence to read: "The 1-year **short-term model** aimed to take account of treatment efficacy and patient adherence…"
16	Section 3.26	"The average cost of psychosocial intervention at £4145 was taken from NICE clinical guideline 115"	Please correct this sentence to read: "The average cost of **secondary care inpatient-assisted withdrawal** at £4145 was taken from NICE clinical guideline 115"
18	Section 3.30	"In all 3 situations, nalmefene plus psychosocial intervention dominated psychosocial intervention alone"	"In **both** situations (**9A and 9B**), nalmefene plus psychosocial intervention dominated psychosocial intervention alone"

19	Section 3.33	"The ERG stated that the evaluation carried out in the model does not meet that specified in the final scope and that it was difficult to know how the results would apply to people receiving different forms and frequencies of psychosocial intervention."	In order to keep this section 3.33 consistent with the discussion at the Appraisal Committee (section 4.9), we suggest the following text could be added to avoid confusion: "The ERG stated that the evaluation carried out in the model does not **fully** meet that specified in the final scope and that it was difficult to know how the results would apply to people receiving different forms and frequencies of psychosocial intervention. **However, the ERG was also of the opinion that the scope cannot be fully evaluated.**"
19	Section 3.34	"The ERG had concerns about the generalisability of the population in the 3 nalmefene studies to clinical practice in England. People with severe psychiatric comorbidities were excluded from all 3 nalmefene trials, and those with severe medical comorbidities were excluded from the ESENSE trials. The manufacturer commented in its submission that many people with alcohol dependence also have diagnosed medical conditions and/or psychiatric comorbidities. Patients were also excluded from the nalmefene trials if they were taking certain medication, such as drugs for angina, anticoagulants, anticonvulsants, insulin, sedatives and systemic steroids. The ERG stated that the safety and efficacy of nalmefene in people taking these drugs was therefore uncertain. Only a small number of trial patients were from the UK (SENSE trial only, 5 sites out of a total of 156) and the manufacturer did not provide any data on the variability of the outcomes for different European countries. The ERG stated that the generalisability of this data for England was unknown."	We would like to reiterate the following points: • In the SENSE clinical trial, including in the five UK trial sites, nalmefene was allowed in patients with stable psychiatric co-morbidity and/or who were taking co-medication. • The decision whether or not to treat with nalmefene has to be taken by the treating physician on an individual basis. • The nalmefene clinical trials were multi-national studies conducted in 19 countries. Nevertheless, the SENSE study included patients from the UK, and these trials are likely to be generalisable to the UK population given that they captured data on different drinking patterns and cultures across Europe. • A comparison of patient baseline characteristics in the nalmefene trials to the United Kingdom Alcohol Treatment Trial (UKATT) in which almost half of patients opted for alcohol reduction as their treatment approach, suggests that patients were reasonably comparable in terms of age, sex, ethnicity, level of alcohol consumption at study baseline, and level of unemployment (see Godfrey C. Cost effectiveness of treatment for alcohol problems: findings of the randomised UK alcohol treatment trial (UKATT). *BMJ* 2005;**331**(7516):544-48; Heather N, Adamson SJ, Raistrick D, Slegg GP. Initial preference for drinking goal in the treatment of alcohol problems: I. Baseline differences between abstinence and non-abstinence groups. *Alcohol and alcoholism* 2010;**45**(2):128-35).
20	Table 2, Comparison 3	"The manufacturer did not comment on the likely cost effectiveness of delayed initiation of nalmefene for people whose alcohol dependence did not respond to psychosocial intervention as recommended in NICE clinical guideline 115, compared with immediate initiation of nalmefene for all patients."	We reiterate that we have no clinical data on the use of nalmefene in people whose alcohol dependence did not respond (first) to PI and thus did not feel able to comment on the cost-effectiveness or otherwise of a delayed initiation strategy.
29	Section 4.6	"The Committee agreed that the relative effectiveness of nalmefene plus psychosocial intervention and naltrexone plus psychosocial	We propose amending this sentence to read: "The Committee agreed that the relative effectiveness of nalmefene plus psychosocial intervention and naltrexone plus psychosocial intervention was uncertain, **due mainly to limitations in the available**

		intervention was uncertain."	**evidence base for naltrexone in people with mild alcohol dependence."**
	Section 5.1	"Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication. "	In response to the specific question posed by NICE in the covering letter to the ACD, we do not believe that any extension to the normal period of 3 months is necessary for the following reasons: **1. Nalmefene is already being prescribed in the UK**. • Nalmefene has been licensed for use in the NHS in the UK since May 2013. The Scottish Medicines Consortium and the All Wales Medicines Strategy Group accepted nalmefene for NHS use in accordance with its licensed indication in November 2013 and January 2014, respectively. • Nalmefene is therefore already being prescribed in clinical practice in England, Wales and Scotland (in both primary care and in specialist settings for suitable patients). **2. Nalmefene is suitable for primary care initiation and prescribing.** • Continuous psychosocial support can be delivered by any healthcare professional and would be comparable to delivering an intervention at the level of an extended brief intervention or 'motivational interviewing' during regular and ongoing patient assessment visits. • The ACD acknowledges that the usual psychosocial intervention provided in clinical practice for mild dependent patients was brief advice or extended brief advice (4.1, p25). The ACD also acknowledges (4.4, p 27) that the clinical specialists' view was that although BRENDA was not used in its entirety in clinical practice, most of its components are provided in the form of brief interventions or extended brief interventions. Finally the committee was satisfied that BRENDA closely represented current clinical practice in England (4.9, p31). **3. Practical implementation of this guidance should not be difficult if the NHS bodies and Local Authorities responsible adopt a pragmatic mindset.** • Although the Appraisal Committee has heard from clinical experts that the recommendations for the provision of psychological support in CG115 are considered to be aspirational, and not reflective of actual clinical practice, the approval of nalmefene allows healthcare professionals to offer a higher level intensity option to treat alcohol dependence than is currently offered in a primary care setting. • The Committee accepted that although NICE clinical guideline 115 recommends a specific intensity, duration and frequency of psychosocial intervention, the usual

			psychosocial intervention provided in clinical practice was brief or extended brief interventions and that both the duration and frequency of these interventions were shorter than that recommended in NICE clinical guideline 115 (section 4.1). The Committee also noted that BRENDA, as described in the three nalmefene studies, most closely resembled current established practice rather than best practice (section 4.4). • Specialist care is not needed to deliver BRENDA-level interventions. GPs and nurses already offer brief advice to patients with alcohol-related problems; they are sufficiently trained, and have the skills base and competence to deliver BRENDA-level interventions (such as extended brief interventions or motivational interviewing) in primary care. This is also supported in NICE CG115 which states that extended brief interventions would be an appropriate level of psychological intervention for treating mild dependence in a generalist tier 2 setting (Raistrick 2006, P85 CG115 full). • The nalmefene Summary of Product Characteristics (SmPC) requirement for continuous psychosocial support should be considered part of a standard clinical interaction and not a significant change from what would be delivered in common practice. Continuous psychosocial support is a simple intervention and is very similar to what is commonly used in routine clinical practice for the management of other long-term or chronic conditions, such as diabetes, where the patient's involvement in decisions about his or her own management and care is important. The psychosocial support needed is similar in level of intensity and duration to a brief intervention or extended brief intervention, as NICE itself has acknowledged. • Finally, as noted above, nalmefene is already being prescribed in the NHS across the UK in a variety of different settings. **4. Lundbeck is supporting the development of services and online psychosocial support offerings.** • To facilitate the introduction of appropriate psychosocial support, Lundbeck has launched an online psychosocial support tool, which is free of charge to the NHS and is available at: www.reduceyourdrinking.com. • Lundbeck has also supported the development of a Psychosocial Support Booklet provided as a service to medicine, for use by healthcare professionals that are less experienced in delivering structured psychosocial support to a patient with mild alcohol dependence