Single Technology Appraisal (STA)

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

MANUFACTURER'S RESPONSE TO ADDITIONAL REQUEST FOR CLARIFICATION

DATED 7th APRIL 2014

- **In the information submitted you have provided a number of scenarios in response to A1 section C and A3. Please could you clarify exactly what you have done in order to produce these scenarios and please ensure the model has been updated with the correct drop down function to clearly demonstrate the calculations.**
- **For question C2, you have confirmed that the formula in the current model is incorrect. Please update the model with the correct formula.**

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.

The model has been corrected. The changes that have been performed are described as follows:

A drop down menu was added to the 'Settings – General' sheet cell B48 titled 'Question C2 – Mortality probability' where the correction can be applied by selecting the option 'As per NICE request'. This drop down menu controls the switch 'switch_mort' which can be found on the 'Data Store' sheet cell B49.

More specifically, the changes performed in the model to apply this option were as follow (cells highlighted in yellow in the model):

Sheet 'Markov Nalmefene', cells:
Q71:104
AJ71:AS104
BX72:CG104
EH72:EQ104
FW72:GF104

Sheet 'Markov MBI', cells:
Q71:104
AK71:AT104

BY72:CH104

Sheet 'Markov Variable treatment', cells:
Q71:104
AJ71:AS104
BX72:CG104
EH72:EQ104
FW72:GF104

Sheet 'Markov No treatment', cells:
Q71:104
AK71:AT104
BY72:CH104

The updated results of the base case analysis taking into account the correction described above are as follows (Table A):

Table A

Scenario	Total costs		Total QALYs		Incremental costs	Incremental QALYs	ICER
	NMF + PI	PI alone	NMF + PI	PI alone			
Base case	£4,445	£4,842	3.624	3.553	-£397	0.071	Nalmefene Dominates

NMF: Nalmefene ; PI:Psychosocial Intervention

***Please note that all results presented in this document were produced with the model corrected re. the feature just described.*

Please be aware that the results presented in the clarification question response document dated 4th April 2014 were produced without this correction. Thus, it will lead to some variations on the results from the same scenario presented in this document, compared to the clarification question response document dated 4th April 2014.

A1.
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.**

In the cost-effectiveness model, we have conducted a scenario analysis which compares nalmefene + psychosocial intervention versus psychosocial intervention consisting of one 60-minute session per week for 12 weeks.

For the nalmefene arm, we kept the same management pattern for the psychosocial intervention provided with nalmefene as in the base case analysis. This highlights that treatment with nalmefene gives the option not only of adding a pharmacological treatment to psychosocial intervention as first-line treatment (post brief intervention), but also gives the option of providing a psychosocial intervention of a lower intensity - with motivational support that can be given in either primary or secondary care as part of a usual medical consultation.

For the treatment cohort with psychosocial intervention consisting of one 60-minute session per week for 12 weeks, we implemented the patient management element in the following way, informed by the economic analysis undertaken for CG115:

- It was assumed that each patient would receive 12 60-minute sessions delivered by a practice nurse. This was costed at £91 per hour of client contact (PSSRU 2012). This was applied during the first 12 weeks of the model.
- Patient drop-outs were considered as equal to those observed during the nalmefene clinical trials.
- It was assumed that all patients would require one initial 30-minute outpatient consultation with a consultant psychiatrist prior to starting treatment. This was costed at £202 (£605/3) (PSSRU 2012).

This scenario analysis resulted in nalmefene + psychosocial intervention still dominating psychosocial intervention alone, leading to even more savings (see scenario 1 of Table B below).

We tested a second scenario where psychosocial intervention alone was costed as described above (scenario 1 in Table B below), but now assuming that 100% of patients treated with nalmefene + psychosocial intervention are treated by a specialist. This does not change the conclusion of the base case that nalmefene + psychosocial intervention dominates (see scenario 2 of Table B below).

Table B

Scenario	Total costs		Total QALYs		Incremental costs	Incremental QALYs	ICER
	NMF + PI	PI alone	NMF + PI	PI alone			
Base case	£4,445	£4,842	3.624	3.553	-£397	0.071	Nalmefene Dominates
Scenario 1	£4,445	£5,933	3.624	3.553	-£1,488	0.071	Nalmefene Dominates
Scenario 2	£4,874	£5,933	3.624	3.553	-£1,059	0.071	Nalmefene Dominates

NMF: Nalmefene ; PI:Psychosocial Intervention

***Please note that all results presented in this document were produced with the model corrected on the feature described under C2 above. This explains the difference of the results presented in this table compared to the ones presented in the clarification question response document dated 4th April 2014.*

What follows is a description of how to reproduce the Table B results in the model:

A drop down menu was added to the 'Settings – General' sheet cell B54 titled 'Question A1C – Intensive MBI Strategy'. This drop down menu controls the switch 'switch_intensMBI' which can be found on the 'Data Store' sheet cell B54.

This switch controls the cost of the Variable Treatment arm (not the MBI arm).

To reproduce Scenario 1:

- Select the option 'As per NICE request' on the Intensive MBI Strategy drop down (Settings – General sheet cell B54)

To reproduce Scenario 2:

- Select the option 'As per NICE request' on the Intensive MBI Strategy drop down (Settings – General sheet cell B54); and on Sheet 'Costs', cell H21, please update to 0%

In terms of providing an indicative ICER when nalmefene is used only in those patients who did not respond to psychological intervention, the clinical data available allows the precise estimation of the cost-effectiveness of the use of nalmefene as first line treatment in addition to psychosocial intervention, compared to psychosocial intervention alone. There are no data available allowing a precise assessment of nalmefene as a second line treatment for patients failing psychosocial intervention.

However, as investigated in Scenario 7 of the MS (section 7.7.10 of the MS), the cost-effectiveness of nalmefene + psychosocial intervention was robust to a substantial increase of effect of psychosocial intervention alone (decrease of relative effect between cohorts). The treatment effect of psychosocial intervention would need to have an increased treatment effect of **70.3% to 77.2%**** for nalmefene + psychosocial intervention not to be cost-effective (at a willingness-to-pay threshold of £20,000 and £30,000) compared to psychosocial intervention alone. Thus, there would need to be a significant decrease in relative effect between nalmefene + psychosocial intervention and psychosocial intervention alone, beyond **70.3% to 77.2%**,** for the implementation of nalmefene + psychosocial intervention not to be cost effective compared to psychological intervention, as second line treatment for patients failing psychosocial intervention. We do not believe this is probable.

*** Results produced with the model corrected on the feature described under C2 above.*

What follows is a description of how to reproduce these threshold results in the model:

This can be reproduced using the 'Variable treatment Effectiveness' slider, sheet 'Settings – General', cells B28 to K28.

This slider controls the switch 'Variable_treatment_slider' which can be found on the sheet 'Data Store' sheet cell B33.

A3.

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.

To investigate the assumption that all patients being in the medium drinking health state after 1 year of treatment would continue with nalmefene, three scenario analyses were performed. In these analyses, the following alternative assumptions of treatment pathways were investigated:

Scenario 1: Patients in the medium drinking health state are assumed to not have responded to treatment and relapse back to high/ very high DRL and thus change treatment strategy to an abstinence-orientated approach (second-line treatment option).

Scenario 2: Patients in the medium drinking health state are assumed to have responded to treatment and are modelled in line with other patients having responded to treatment in the controlled-drinking health state.

Scenario 3: An extreme scenario against nalmefene where patients in the medium drinking health state in the nalmefene + psychosocial intervention arm are modelled to have not responded (as scenario 1) and patients in the psychosocial intervention alone arm are modelled to have responded (as scenario 2).

All three scenarios showed that the cost-effectiveness conclusion is not sensitive to varying this model feature. Table C below details the results for the three tested scenarios. For scenario 3, extreme scenario against nalmefene, the ICER is still well below the £20,000 threshold.

Table C

Scenario	Total costs		Total QALYs		Incremental costs	Incremental QALYs	ICER
	NMF + PI	PI alone	NMF + PI	PI alone			
Base case	£4,445	£4,842	3.624	3.553	-£397	0.071	Nalmefene Dominates
Scenario 1	£4,803	£5,240	3.608	3.538	-£437	0.070	Nalmefene dominates
Scenario 2	£4,218	£4,559	3.638	3.570	-£341	0.068	Nalmefene dominates
Scenario 3	£4,803	£4,559	3.609	3.570	£244	0.039	£6,280/QALY

NMF:Nalmefene ; PI:Psychosocial Intervention

***Please note that all results presented in this document were produced with the model corrected on the feature described under C2 above. This explains the difference of the results presented in this table compared to the ones presented in the clarification question response document dated 4th April 2014.*

What follows is a description of how to reproduce the Table C results in the model:

Two drop down menus were added to the 'Settings – General' sheet.

Cell B36 contains the drop down menu titled 'Question A3 – Medium drinking (long term) – Nalmefene' that controls the switch 'switch_medDRL_nalm' which can be found on the 'Data Store' sheet cell B39.

Cell B42 contains the drop down menu titled 'Question A3 – Medium drinking (long term) – MBI' that controls the switch 'switch_medDRL_MBI' which can be found on the 'Data Store' sheet cell

B44.

To reproduce Scenario 1:

- ‘Settings – General’ sheet, cell B36, select ‘Scenario 1 (transition to high and very high DRL)’
- ‘Settings – General’ sheet, cell B42, select ‘Scenario 1 (transition to high and very high DRL)’

To reproduce Scenario 2:

- ‘Settings – General’ sheet, cell B36, select ‘Scenario 2 (transition to controlled drinking)’
- ‘Settings – General’ sheet, cell B42, select ‘Scenario 2 (transition to controlled drinking)’

To reproduce Scenario 2:

- ‘Settings – General’ sheet, cell B36, select ‘Scenario 1 (transition to high and very high DRL)’
- ‘Settings – General’ sheet, cell B42, select ‘Scenario 2 (transition to controlled drinking)’