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Clarifications to Evidence Review Group's report

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Vortioxetine for treating major depressive disorder

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This document responds to a request for clarification from the manufacturer on some aspects of the additional analysis undertaken by the ERG.

Manufacturer request: *"…we are finding it impossible to replicate the results based only on the changes in utilities that have been specified in Table 50 of their report and the text that accompanies this."*

ERG's Response:

Overview of the rational for the changes made

- The ERG changed not only the values of inputs, but also modified the way in which inputs were used in the decision model
- Relapse has been defined is the literature as "the return of symptoms meeting the full syndrome criteria that occurs during an asymptomatic period of incomplete recovery from the index episode" [Bakish (2001) with reference to Frank (1991)].
- The ERG made 3 changes to the manufacturer model.
  i. As part of the ERG corrections, the relapse utility was assumed to be the same as the baseline utility for depression, which the ERG considers to better represent the definition provided above.
  ii. In the MS, patients achieving remission in the acute phase, but relapsing in the maintenance phase, are assumed to relapse three months into the maintenance phase. The MS, however, assigned these patients the relapse utility for the first three months in maintenance phase, and switched them to the Markov component after that. The ERG modified the MS model by assigning three months utility of remission, rather than utility of relapse, to describe the time before the relapse occurs.
  iii. In the Markov component of the MS, no distinction is made between patients that have switched due to lack of efficacy and patients that relapsed – in both situations patients are

assigned the utility of relapse. The ERG believes that patients not achieving remission on active therapy will have different utilities to those relapsing. The ERG attempted to reflect this distinction.

Detailed description of the corrections made

i. The ERG changed the utility values used as inputs, as detailed in table 50 of the ERG report.
ii. Within the decision tree, patients who relapse after three months were given utility of remission for the first three months in the maintenance phase, before relapsing and entering the Markov component of the model. This was done by editing the cells in column DT in sheets 'DT – Vortioxetine' and 'DT – Comparator'. For instance, the cell DT15 contained the formula '=Utility_remission_after_2months*(3/12)*$Z15' instead of '=Utility_relapse_after_2months*(3/12)*$Z15'.
iii. The changes made to the Markov component of the model were as follows:
    - Patients relapsing after three months in the maintenance phase of the decision tree did not enter the sheet 'Markov – switch LOE' and instead entered a newly created sheet 'Markov – switch relapse'. In the first instance, this was simply a copy of 'Markov – switch LOE'.
    - All Markov sheets were edited to reflect that patients entering a 'No remission …' health state had different utilities depending upon they were relapsing following a remission, or whether they were not remitting.
    - For 'No remission 3rd line' this was a case of editing the Markov utilities tables for the 'Markov – switch LOE' and 'Markov – switch AE' tabs, cells F57:F62 so that they had, for example in cell F57, the formula '=(F44/2+F45/2)*Utility_no_remission_8weeks*2/12' instead of '=(F44/2+F45/2)*Utility_relapse_after_2months*2/12'. Note that tabs 'Markov – switch relapse' and 'Markov – switch long term AE' were not changed for 'No remission 3rd line' health state.
    - For 'No remission 4th line' and 'No remission 5th line', the formulae could no longer be based on the Transition matrix table, since the numbers contained in these could contain both relapsers and non-remitters. As a result, it was necessary to multiply the relevant rows and columns of the matrices by hand and assign different utilities to each. See formulae contained within L57, L58, R57 and R58 on 'Markov – switch LOE', 'Markov – switch AE' and 'Markov – switch relapse' tabs, and L59, L60, R59 and R60 of 'Markov – switch long term AE'.

Calculations on total costs and utilities were also modified to reflect the changes above.

For clarity, we also provide the updated Excel model file. Note that this file was not prepared for external use.

Manufacturer request: *"Would it be possible to provide further clarification on the exploratory analyses related to efficacy in subsequent lines of treatment (section 6.3.2) that you described on page 136 of the ERG report? "*

ERG's Response:

Exploratory analyses regarding remission and relapse for 3rd, 4th and 5th line treatments

For the exploratory analyses, remission rates in 3rd, 4th and 5th lines were calculated by taking the average of the non-vortioxetine treatments' remission rates (table 58, ERG report) and also by taking these values and applying a proportionate reduction based on STAR*D (table 59, ERG report). The values used are detailed in the following tables.

Table 1 Remission inputs for Table 58, ERG report

	MS	Llorca	IE	Pae
2nd line	28.15%	42.37%	40.50%	39.43%
3rd line	28.15%	42.37%	40.50%	39.43%
4th line	28.15%	42.37%	40.50%	39.43%
5th line	28.15%	42.37%	40.50%	39.43%

Table 2 Remission inputs for Table 59, ERG report

	MS	Llorca	IE	Pae
2nd line	28.15%	42.37%	40.50%	39.43%
3rd line	12.60%	18.97%	18.13%	17.66%
4th line	11.96%	18.00%	17.21%	16.75%
5th line	11.96%	18.00%	17.21%	16.75%

The relapse rate used was based on Limosin (2004) [1]using a calculation to convert from a 6-month rate to a 2-month rate assuming that the rate is constant:

$$p_{L\ 2-month} = 1 - \exp\left(\frac{\ln(1 - p_{L\ 6-month})}{3}\right)$$

[1] Limosin (2004) was used as an alternative to STAR*D as it was considered to better reflect the population for the decision problem and is consistent with the source employed in the decision tree.

This resulted in a value of $p_{L\ 2-month} = 0.0498$.