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Vortioxetine for the treatment of major depressive disorder [ID583]

NICE Single Technology Appraisal

ERG review of manufacturer's response to the Appraisal Consultation Document

10 of August 2015

Overview

This document comments on the manufacturer's response to the Appraisal Consultation Document (ACD) and to requests for additional analyses by the Committee. In this response the manufacturer included additional evidence and a revised economic model to inform the cost-effectiveness of vortioxetine. Importantly, the revised model now focuses on a separate decision problem from the original submission based on the Committee's request for additional analyses to inform the clinical and cost-effectiveness of vortioxetine for use in 3rd line treatment and onwards. Hence, the manufacturer's revised model now evaluates: *"… the cost-effectiveness of vortioxetine in patients with a major depressive episode (MDE) who have experienced an inadequate response (either due to efficacy or intolerability) to* ***2 or more*** *previous antidepressants."*. Besides, the manufacturer also incorporated significant structural revisions to the economic model and further considered the relevance of previous assumptions and data.

The ERG was requested by NICE to provide additional commentary and validity checks on this additional evidence submitted by the manufacturer. Due to the limited resource available, the additional work undertaken by the ERG does not constitute a formal critique of the manufacturer's resubmission and hence does not accord with the procedures and templates applied to the original submission.

The ERG considers that most concerns raised by the committee have been addressed by the manufacturer. The ERG believes the revised model more accurately reflects the nature of treatment decisions and outcomes in MDD, and that the revisions have broadly been implemented using the appropriate available data.

The further changes can be described in five key areas of uncertainty:

1. Sources of evidence for efficacy inputs: The manufacturer has considered five alternative sets of efficacy inputs for use in the revised model. These are in line with the scenarios presented by the ERG in their report. The manufacturer's preferred analysis assumes equal efficacy across treatment. The manufacturer also uses their original analyses based on a network meta-analysis including only studies in the switch population (second line), and two alternative meta-analyses: Pae [ref] and Llorca et al. (2014). They have also provided a new clinical source – the SOLUTION trial. These are discussed further in the critique section of this review.
2. Model structure incorporating response: The manufacturer modified the model to consider outcomes at 8 and 12 weeks. As previously, remitters are assumed to enter in maintenance phase. In the revised analyses responders at 8 weeks continue treatment and if response is not lost at 12 weeks they are assumed to move into maintenance phase.
3. Model time horizon of 24 months (instead of 12 months). All analyses of the revised model assume a 24 month time horizon, where in the original submission a 12 month time horizon had been assumed.
4. Inclusion of recurrence after recovery: Following successful maintenance treatment patients enter recovery. In the manufacturer's original analysis patients were not at risk of recurring when in recovery but in the revised analyses they are (0.44% risk assumed for 2 months, corresponding to a 10 year probability of 23.2%), in which case they are switched onto a successive line of treatment.
5. Treatment initiation and maintenance in primary or secondary care: The manufacturer assumed a primary care for their revised base case, but explored the possibility of secondary care initiation and maintenance in scenario analysis.

The revised manufacturer's model was run for a number of alternative scenarios reflecting uncertainties around model structure, duration of maintenance treatment, setting of care, resource use of patients achieving response without remission and inclusion of recurrence. The included scenarios are represented in Table 1 and

Table **2**.

Table 1 Summary of analyses presented with response and remission model

Structure/inputs	Response and remission model								
	Analyses Set 1 Up to 6 months maintenance treatment; probability of recurrence			**Analyses Set 2** Up to 22 months maintenance			**Analyses Set 3** Up to 6 months maintenance; no risk of recurrence		
	1a [BC]	1b [AA]	1c [AA]	2a [AA]	2b [AA]	2c [AA]	3a [AP]	3b [AP]	3c [AP]
Maintenance treatment length									
Up to 6 months	x	x	x				X	X	x
Up to 22 months				x	x	x			
Recurrence									
Risk of recurrence in the recovery phase	x	x	x						
Resource use									
Response = remission	x	x		x	x		X	X	
+30% for response over remission			x			x			x
Treatment setting									
Primary care initiation and maintenance	x		x	x		x	X		x
Secondary care initiation and maintenance		x			x			X	

BC = Base-case; AA = additional analyses presented in this section; AP = analyses included in Appendix 6.11.

All analyses will be run for all data sets: Par efficacy (base-case); SOLUTION; Switch network; Llorca (2014) and Pae (2014)

Table 2 Summary of analyses presented with remission only model

Structure/inputs	Remission model					
	Analyses Set 4		Analyses Set 5		Analyses Set 6	
Maintenance treatment length	4a [AP]	4b [AP]	5a [AP]	5a [AP]	6a [AP]	6b [AP]
Up to 6 months	x	X			X	x
Up to 22 months			x	x		
Recurrence						
Risk of recurrence in the recovery phase	x	X				
Resource use						
Response = remission	x	X	x	x	X	x
+30% for response over remission						
Treatment setting						
Primary care initiation and maintenance	x		x		X	
Secondary care initiation and maintenance		X		x		x

BC = Base-case; AA = additional analyses presented in this section; AP = analyses included in Appendix 6.10

All analyses will be run for all data sets: Par efficacy (base-case); SOLUTION; Switch network; Llorca (2014) and Pae (2014)

- The **base case** corresponds to scenario 1A and assumes treatment continuation based on both response and remission, 6-month length of maintenance phase, the risk of recurrence as described above and primary care initiation and maintenance.

- Analysis sets 1, 2 and 3 consider models where have both response and remission.
- Analysis sets 4, 5 and 6 consider models with remission only.
- Analysis sets 2 and 5 assume that maintenance lasts up to 22 months.
- Analysis sets 3 and 6 assume a zero probability of recurrence after recovery.
- In the scenarios denoted with B, treatment is initiated and maintained in secondary care.
- In the scenarios denoted with C, patients in response are assumed to have 30% greater resource use than patients in remission.
- Note that within each of the scenarios, analyses are run for the 5 relative effectiveness.

Among these, the ERG considers that analysis sets 1 and 2 are particularly informative since they incorporate all changes to model structure and both contain reasonable assumptions regarding the duration of maintenance treatment. Of these, scenarios A, B and C are again all useful for exploring uncertainty around setting and resource use assumptions. As a consequence, analysis sets 4 and 5 provide a clear demonstration of the impact on cost-effectiveness of not including response as a relevant clinical outcome. Similarly, analysis sets 3 and 6 demonstrate the effect of excluding recurrence in the revised model.

ERG commentary

a. Manufacturer's critique of use of Llorca et al. (2014)

The manufacturer notes that in the Llorca review a high number of studies did not report data on response or remission and concludes there is the potential for reporting bias. The ERG considered in their report the primary outcome in Llorca, the standardised mean difference in depression score, (see Table 26 of ERG report), which is less prone to missingness and therefore to bias. Results on this outcome show there was no statistically significant difference in effect between vortioxetine and any other treatment. This finding was consistent with results for response rate and remission. Hence the ERG considers that there is no evidence to suggest that there is any reporting bias in the Llorca review.

b. The SOLUTION trial

Based on the information provided in Appendix two of the response to ACD, the ERG considers SOLUTION to have been a well-conducted RCT. The trial was entirely conducted in an East-Asian population, not representative of the UK, but the ERG agrees that it is unlikely that the relative effects between vortioxetine and venlafaxine groups would differ substantially in the UK.

Vortioxetine was found to be not inferior to venlafaxine, and results were consistent with an assumption that vortioxetine and venlafaxine have the same response and remission rates. There was some evidence that vortioxetine is more tolerable, with lower rates of withdrawal, and possibly lower rates of adverse events.

This trial supports the ERG's original conclusions that vortioxetine is of similar efficacy to other non-SSRIs, but may be more tolerable, and also the results of the Llorca review. It contradicts the original network analysis presented by the manufacturer, where venlafaxine was found to be less effective than vortioxetine in both remission and response rates (see ACD response Table 5).

c. Revised model structure

The initial model submitted by the manufacturer considered treatment continuation to be dependent only on remission at 8 weeks. However, both the committee and the ERG highlighted the importance of response in determining treatment decisions, and as a consequence the manufacturer incorporated this clinical outcome into their revised model structure.

Figure 1 below describes the revised structure of the acute phase model (from manufacturer's response to ACD). The diagram shows that a proportion of patients who do not achieve remission at 8 weeks respond to treatment, and are kept on the same line of therapy for a further 4 weeks. Patients no longer responding to treatment after the 12 weeks are switched onto 4th line therapy. Having achieved remission at 8 or 12 weeks, or response at 12 weeks, they will maintain on the same treatment for up to 6 months (maintenance). Patients are at risk of withdrawing due to adverse events during the whole of the acute phases (12 weeks), but when they do withdraw it is assumed they do so after 4 weeks of treatment on 3rd line. Costs and disutilities are, however, incurred in the first 8 weeks.

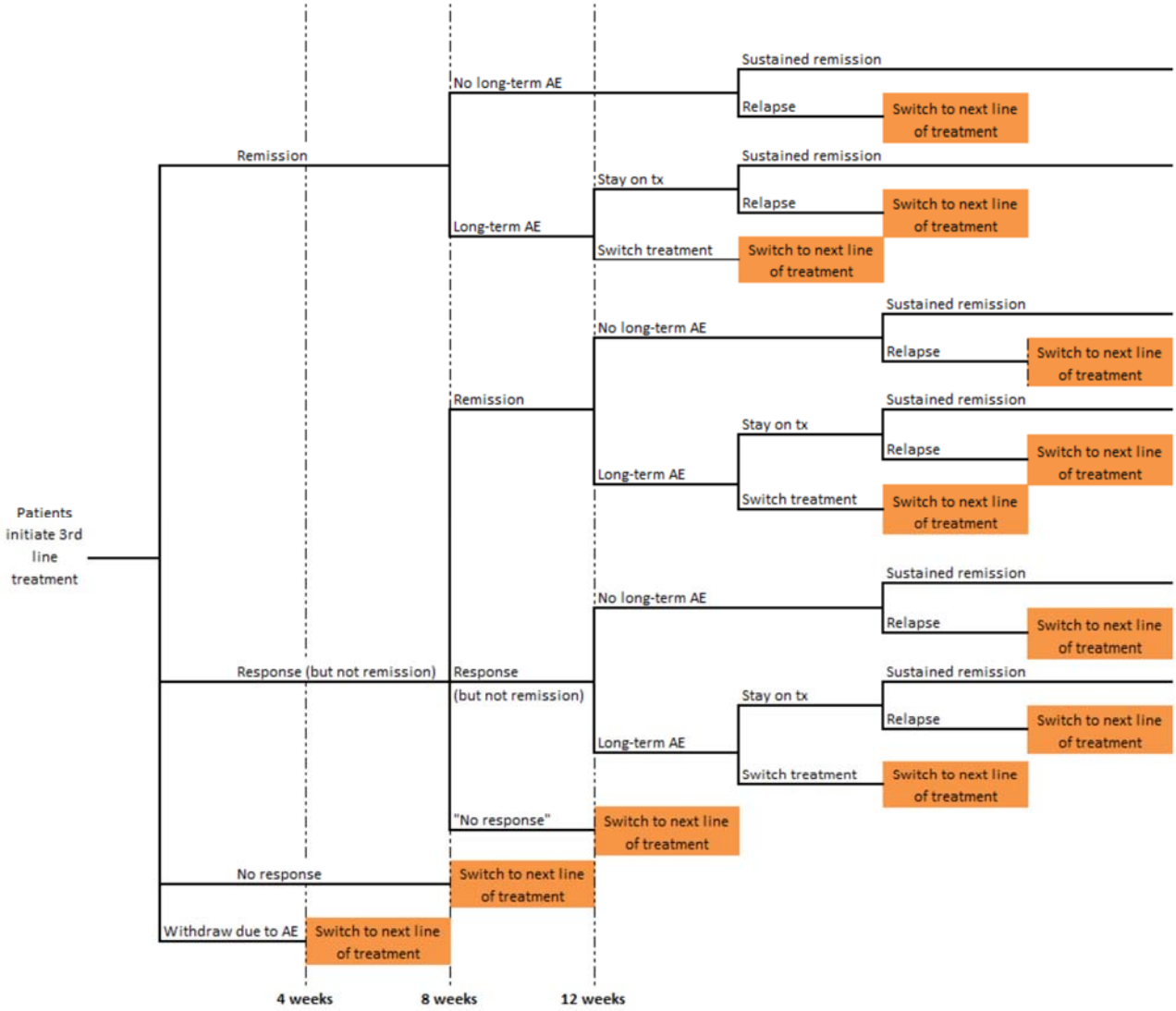

Figure 1 Revised decision tree structure for the acute phase

These changes imply the use of additional data and/or assumptions in the revised model for the subgroup of responders (non-remitters):

(i) The probability of a patient being a responder at 8 and 12 weeks were calculated from conditional probabilities observed in REVIVE. For 12 weeks, 59.52% of patients in REVIVE were remitters and 32.14% were responders (but not remitters) (Table 6 in response to ACD). Due to absence of data for comparators, the manufacturer assumed these to be the equal across all treatments.

(ii) Response without remission is assigned a different utility value taken from REVIVE (Table 8 in response to ACD).

(iii) The manufacturer found no evidence regarding resource use for responders and thus assumed equal level of resource use to patients in remission. To test this assumption the manufacturer assigns 30% higher costs to responders in scenarios analysis (scenarios 1C, 2C and 3C).

The impact of excluding response as a clinical outcome in the decision model can be seen by comparing analysis set 1 with analysis set 4, analysis set 2 with analysis set 5 and analysis set 3 with analysis set 6. In most cases, including response is favourable towards the estimated cost-effectiveness of vortioxetine.

d. Adjustment of baseline probabilities to reflect 3rd line use

The original analyses used an absolute probability of remission for vortioxetine from the REVIVE trial. Relative treatment effects for the comparators would then be applied to this value. In order to reflect the fact that the decision problem is now considering 3rd line treatment, the manufacturer adjusted the absolute probabilities of response, remission and no-response on vortioxetine. The adjustment was based on a proportionate reduction of the REVIVE numbers based on the proportionate reduction from 2nd to 3rd line observed in STAR*D trial (Rush et al., 2006) – see Table 4 in response to ACD. The adjusted probability of a patient remitting after 3rd line with vortioxetine is now assumed at 18.1% (decreased from 40.5% in the original submission for 2nd line), and the probability of no response at 44.8% (increased from 38.5% in the original submission for 2nd line). Note that no adjustment needed to be made to the probability of response without remission since this was the residual probability after accounting for remission, no response and withdrawal due to AEs. Also note that the probability of withdrawing due to AEs was not assumed to differ between 2nd and 3rd line.

e. Revised model time horizon of 24 months

The original analyses (both by manufacturer and ERG) assumed a 6 month maintenance treatment and employed a time horizon of 12 months, justified as being sufficient to capture the health outcomes. A 24 month maintenance treatment duration (in patients with previous history) was considered in scenario analyses, and the time horizon was, in this scenario only, extended to 24 months. The manufacturer's revised model, however, now employs a 24 month time horizon even in analyses that consider maintenance therapy to last for only 6 months. The justification for this change is not presented.

The ERG expects that, by employing a time horizon of 24 months as opposed to 12 months, the cost-effectiveness of vortioxetine in the equal efficacy scenario will be improved against most comparators, since it has a better tolerability profile that leads to fewer patients switching treatment in the acute and maintenance periods of the model and thus entering the Markov component of the model. Note that with the decision problem having changed to 3rd line of treatment, a lower proportion of patients are assumed to respond to initial treatment and thus the average duration of MDE assumed in the model is much higher than in the previous submission. As a matter of fact, within the revised base case, more than 30% of patients will not be in remission at 24 months. Indeed the ERG had previously raised an issue with the face validity of the manufacturer's model – the average duration of an MDE was estimated to be at least 6.73 months in the MS, compared to untreated episodes lasting 5 to 6 months (WHO, 2008).

f. Assumptions about 4th, 5th and 6th line treatments

Within the manufacturer's model there are a number of situations that lead to patients switching onto successive lines of treatment, i.e. 4th line of treatment onwards, and enter the Markov component of the

model with parameters taken from the STAR*D study (Rush et al., 2004). The revised model submitted by the manufacturer does not update the Markov model parameters – Table 3. Thus the 4th line parameters in the model are taken from the estimates relating to 3rd line treatment in STAR*D. Also, the use of STAR*D was criticised in the initial ERG report, and a number of sensitivity analyses were carried out by the ERG in section 6 of the ERG report that explored the implications of using these parameters for cost-effectiveness estimates. These were not reflected in the revised manufacturer analyses.

Table 3 Probabilities for Markov component concerning successive lines of treatment

Probability	Value	Source
3rd line remission	18.10%	Adjusted REVIVE using STAR*D
4th line remission	13.70%	STAR*D (3rd line)
5/6th line remission	13.00%	STAR*D (4/5th line)
4th line relapse	24.98%	STAR*D (3rd line)
5/6th line relapse	42.57%	STAR*D (4/5th line)

If equal efficacy is assumed, a worsened prognosis for patients switching treatment will improved relative cost-effectiveness of vortioxetine as this drug is more tolerable than most comparators.

g. Inclusion of recurrence

Patients entering the recovery health state in the original MS and ERG-corrected model were assumed to have no further risk of MDD during the time horizon of the model. In the response to ACD model, patients who achieve recovery (after two months in recovery) face a two-month probability of recurrence of 0.44% that is constant over time (this means 2.6% will have a recurrence in a year and 5.1% in 2 years). This value was derived from a published paper (Hardeveld, 2013) that analysed a subsample of The Netherlands Mental Health Survey and Incidence Study (NEMESIS), a general population survey with 3 waves of interviews (at time 0, 12 months after the first and 3 years after the first). The subsample included 687 subjects that had recovered from MDD (participants had to be in remission for at least 6 months). The study reports cumulative recurrence of MDD to be 13.2% at 5 years, 23.2% at 10 years and 42.0% at 20 years. These equate to a 2-monthly probability of recurrence of 0.47%, 0.44% and 0.45%, respectively, suggesting that the likelihood of recurrence is constant over the 20 years. The manufacturer used the results for 10 year time period, and given the apparent constant rate between 5 and 20 years, the ERG believes this to be reasonable given the evidence presented.

h. Commentary on cost-effectiveness results

The results presented in Table 4 are for the manufacturer's preferred assumptions regarding efficacy in the revised base case model (1A). They show that vortioxetine is found to have an ICER of £4,590 per QALY relative to citalopram with agomelatine having a large ICER of £243,079 per QALY relative to vortioxetine. When SSRIs are excluded from the comparison, vortioxetine dominates all other comparators with the exception of agomelatine, which has an ICER of £243,079 per QALY relative to vortioxetine.

Table 4 Base case results assuming par efficacy

1A	Total costs (£)	Total QALYS	Incremental ICERs (including SSRIs)	Incremental ICERs (*excluding SSRIs*)
Scenario: Equal efficacy				
Citalopram	1342	1.414	ref	n/a
Escitalopram	1347	1.414	Dominated	n/a
Sertraline	1357	1.412	Dominated	n/a
Vortioxetine	1399	1.427	£4,590	ref
Venlafaxine	1400	1.41	Dominated	Dominated
Duloxetine	1549	1.411	Dominated	Dominated
Agomelatine	1567	1.428	£243,079	£243,079

The results from the revised base case model are sensitive to the efficacy inputs and different clinical sources that might be used to inform these parameters. Results when using different sets of evidence are shown below in Table 5.

Table 5 Results for base case model using different sources of evidence and assumptions regarding efficacy parameters

1A	Total costs (£)	Total QALYS	Incremental ICERs (including SSRIs)	Incremental ICERs (*excluding SSRIs*)
Scenario: SOLUTION				
Vortioxetine	1393	1.427	ref	ref
Venlafaxine	1443	1.399	Dominated	Dominated
Scenario: SWITCH				
Vortioxetine	1399	1.427	ref	n/a
Sertraline	1648	1.33	Dominated	ref
Venlafaxine	1649	1.336	Dominated	Dominated
Agomelatine	1690	1.38	Dominated	Dominated
Scenario: Llorca (2014)				
Escitalopram	1299	1.431	ref	n/a
Venlafaxine	1331	1.431	£41,999	ref
Vortioxetine	1394	1.427	Dominated	Dominated
Duloxetine	1526	1.424	Dominated	Dominated
Agomelatine	1582	1.424	Dominated	Dominated
Scenario: Pae (2014)				
Vortioxetine	1399	1.427	ref	ref
Venlafaxine	1404	1.41	Dominated	Dominated
Duloxetine	1469	1.445	£3,878	£3,878
Agomelatine	1696	1.378	Dominated	Dominated

The use of the Llorca (2014) evidence set leads to very different results. In the base case model, vortioxetine is dominated by venlafaxine when Llorca et al (2014) estimates are used for efficacy parameters. Indeed in all of the 15 scenarios regarding model structure this result holds. Using Pae et al (2014) is shown to alter results also, with duloxetine more effective than vortioxetine resulting in an ICER of £3,878. According to SOLUTION and SWITCH vortioxetine is found to be dominant, i.e. cheaper and

more effective than all comparators. As a result, the choice of efficacy parameters and the degree of belief placed in each is crucial to determining the appropriate conclusions regarding vortioxetine's cost-effectiveness as a third-line treatment for a MDE.

In most cases, conclusions are not changed between different analysis sets as much as they are by considering different sources of evidence (which is illustrated above). Scenario 2A considers an extended duration of maintenance treatment of 22 months, but otherwise represents the manufacturer's revised base case model. This scenario is particularly relevant for patients with a history of MDEs where NICE CG90 suggests maintenance for at least two years.

Table 6 Results from analysis 2A (up to 22 months maintenance)

2A	Total costs (£)	Total QALYS	Incremental ICERs (including SSRIs)	Incremental ICERs (*excluding SSRIs*)
Scenario: Equal efficacy				
Citalopram	1659	1.408	ref	n/a
Escitalopram	1670	1.407	Dominated	n/a
Sertraline	1682	1.405	Dominated	n/a
Venlafaxine	1778	1.403	Dominated	ref
Vortioxetine	1923	1.419	£22,664	£8,846
Duloxetine	2184	1.404	Dominated	Dominated
Agomelatine	2312	1.42	£700,807	£700,807
Scenario: Llorca (2014)				
Escitalopram	1644	1.423	ref	n/a
Venlafaxine	1754	1.425	£45,254	ref
Vortioxetine	1918	1.419	Dominated	Dominated
Duloxetine	2195	1.417	Dominated	Dominated
Agomelatine	2306	1.415	Dominated	Dominated

Table 6 shows the results for scenario 2A when either equal efficacy or Llorca et al. (2014) evidence sets are used for efficacy parameter inputs. Vortioxetine is dominated in all scenarios with the Llorca et al. (2014). With equal efficacy vortioxetine remains the second most effective treatment, but is found to be the third most costly as opposed to fourth in 1A. This is due to the high acquisition costs of vortioxetine. As a result, it's ICER relative to citalopram is now £22,664 per QALY (compared to £4,590 per QALY in 1A). When computing results against comparators excluding SSRIs, vortioxetine no longer dominates venlafaxine as in 1A, but is more costly and so has an ICER relative to venlafaxine of £8,846 per QALY. Similarly in results with other evidence sets, vortioxetine goes from being the cheapest treatment to being more expensive than venlafaxine. For example in the SOLUTION scenario vortioxetine has an ICER of £5,054 per QALY in 2A when was dominant in 1A.

Cost-effectiveness results from the other scenarios in analysis set 2 (extended duration of maintenance period), with par efficacy assumption applied, are similar to those presented above from 2A. Vortioxetine is associated with a positive ICER in all cases as is found to be more costly than venlafaxine and the value of the ICER is increased significantly relative to citalopram when include SSRIs as relevant comparators.

Scenario 2B, where care is initiated and maintained in secondary care, results in better cost-effectiveness for vortioxetine relative to scenario 2A. The inclusion of an additional 30% resource use by responders worsens the cost-effectiveness of vortioxetine in 2C compared to 2A.

Within analysis set 1, scenario 1B (secondary care) also improves the cost-effectiveness of vortioxetine compared to 1A. In fact, it becomes the cheapest treatment with the par efficacy assumption and so dominant over all comparators except for agomelatine, which has a high ICER of £332,296. When responders are assumed to have 30% more resource use (1C) the results are less favourable in terms of the cost-effectiveness of vortioxetine and it becomes more costly than venlafaxine. Nevertheless, when excluding SSRIs, vortioxetine has an ICER of £26 per QALY relative to venlafaxine.

i. Systematic review of relative efficacy

In Appendix 6.2 the manufacturers presented a review to identify evidence as to whether treatment effects vary between initial and switch populations. Most included studies were small crossover trials that the ERG considers cannot accurately represent real switching populations, and most trials evaluated tricyclic or tetracyclic antidepressants that have not been considered in the submission and are not in general first-line use.

Only the included meta-analysis by Bauer et al (2009) compared first-line and post-switch treatments, and showed some evidence that venlafaxine is relatively more effective than alternatives (probably SSRIs) in switch patients than in first-line therapy when compared to SSRIs. It should be noted that because not all control group switch patients received SSRIs there is potential for bias in these results. This supports the evidence in the Papakostas meta-analysis in the original manufacturer's submission, which showed that, in people switching from an SSRI, using a non-SSRI was more effective that another SSRI.

None of this addresses the ERG's original concern: whether the relative efficacy of the non-SSRIs in the submission (vortioxetine, venlafaxine, duloxetine etc.) varied between pre-and post-switch populations. This review found no evidence comparing these non-SSRIs, so it is reasonable to assume there is currently no such evidence. Therefore, considering all evidence comparing non-SSRIs (such as the Llorca review) is appropriate.