



Cost-effectiveness of vortioxetine (Brintellix®) for the treatment of major depressive disorder (MDD) in adults.

The NCPE has issued a recommendation regarding the cost-effectiveness of vortioxetine (Brintellix®). Following NCPE assessment of the applicant's submission, vortioxetine (Brintellix®) is not considered cost-effective for the treatment of major depressive disorder in adults and therefore is not recommended for reimbursement.

The HSE asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the applicant's (Lundbeck) economic dossier on the cost effectiveness of vortioxetine (Brintellix®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

Summary

In February 2016, Lundbeck submitted a dossier for vortioxetine (Brintellix®) which is indicated for the treatment of major depressive disorder in adults. The licensed indication is broad, and therefore potentially encompasses all adults who have major depressive disorder (MDD).

1. Comparative effectiveness of vortioxetine (Brintellix®)

The applicant's submission positioned vortioxetine in the 3rd line setting. Therefore the clinical evidence supporting the economic evaluation focussed on trials in patients who had previously received antidepressants for a current major depressive episode (MDE) but were switching treatment to vortioxetine due to a lack of response or adverse events; what they termed a 'switch' population. The Review Group (RG) noted that this was a substantial restriction when compared to the licensed indication, which specifies a general population of all adults with MDD.

The applicant presented several data sources to inform the relative efficacy of vortioxetine compared to other ADs. A network of evidence was provided by the applicant for the 'switch' population which included four trials only. The RG were concerned with the reliability of the network analysis and that it did not provide valid evidence from which any conclusion on the efficacy of vortioxetine could be drawn. A direct comparison of vortioxetine to venlafaxine (SOLUTION) was also presented by the applicant. However the RG considered it was of limited generalisability to the Irish population and noted that the results conflicted with other studies comparing vortioxetine with venlafaxine (Llorca *et al.*, 2014; Meeker 2015). A further indirect treatment comparison (Llorca *et al.*, 2014) was provided. This was a meta-regression analysis sponsored by the applicant. The analysis generally found no statistical significant evidence of a difference in efficacy between vortioxetine and any other treatment. An additional meta-analysis (not sponsored by the company) of RCTs with active reference treatment arms was also provided (Pae *et al* 2014). The applicant therefore proposed an assumption for populating the efficacy inputs for all comparators in the model, based on equal or 'par efficacy'. This assumption assumed no difference in efficacy between vortioxetine and comparators, although tolerability

differences between treatments were considered. The applicant used this parameter for treatment efficacy in their base case analysis (i.e. 3rd line setting). The RG concluded that on the basis of the evidence presented in the submission that the Llorca study may represent the most reliable evidence for comparing vortioxetine to other treatments. The ‘*par efficacy*’ assumption was also used in RG analyses.

2. Safety of vortioxetine (Brintellix®)

The applicant conducted a literature review in which they assimilated safety evidence from short term placebo controlled studies and from open label long term continuation studies. The analysis of the pooled placebo controlled studies and the analysis of the pooled continuation studies included relatively large patient numbers and showed broadly comparable results. Although the incidence of AEs was high in patients receiving vortioxetine, most AEs were mild to moderate in intensity and there was no conclusive evidence that these were dose-dependent.

Both pooled analyses had limitations. All analyses from the pool of continuation studies were uncontrolled, and as such are at a high risk of confounding. All continuation studies were one year extensions, and nearly half of patients received vortioxetine for less than one year, which is significantly less than for patients for whom maintenance may be recommended for two years or more. Some relevant studies may have been missed, since only studies that reported safety as a primary outcome were included. In conclusion, data on adverse events with vortioxetine, particularly when compared to other antidepressants, are too limited to draw any firm conclusions on the safety of vortioxetine.

3. Cost effectiveness of vortioxetine

The applicant presented a cost utility analysis which estimated the cost-effectiveness of vortioxetine in the 3rd line setting. A first and second line setting were presented as sensitivity analyses. The comparators considered in the model were citalopram, venlafaxine, escitalopram, agomelatine, sertraline and duloxetine, all of which could be considered relevant to the healthcare payer. In the base case results presented by the applicant, vortioxetine dominated all comparators.

The RG considered that the restriction to consider a ‘switch’ population only was not

in line with the licensed indication and constrained the evidence presented in both the clinical and cost effectiveness analyses. The RG then estimated the cost effectiveness of vortioxetine using a preferred set of model inputs, which were as follows; using data from Llorca *et al* (2014) as a source of evidence for treatment efficacy, setting the probabilities for long term adverse events to the same as the comparator and for treatment management after long term adverse events, varying the proportions of patients who stay on treatment, who get their treatment adjusted and who switch. Changing the model parameters as outlined above resulted in vortioxetine being dominated by the comparators in the 1st and 3rd line setting with the exception of the comparison with duloxetine in the 3rd line setting which resulted in an ICER of €3,210,230.

Probabilistic sensitivity analysis

A probabilistic analysis was conducted by the applicant, giving the following results (for the 3rd line setting); for the agomelatine comparison, vortioxetine had a 47.1% probability of being cost effective at a threshold of €45,000/QALY. For the comparisons with venlafaxine, sertraline, citalopram, escitalopram and duloxetine, the probability of vortioxetine being cost effective at a threshold of €45,000/QALY ranged from 76.9% to 86.8%.

4. Budget impact of vortioxetine

The price to wholesaler of vortioxetine for the 10mg, 15mg and 20mg 28 tablet dose packs are as follows; €33.25, €47.92 and €57.70. Vortioxetine is more expensive than the comparators, with the exception of agomelatine.

The applicant gives an estimate of 58,156 for the total population eligible to receive a third line AD, as well as providing utilisations estimates, in terms of defined daily doses (DDDs). A total usage in Ireland of ADs for the period July 2015-June 2016 is estimated at 96,166,679 DDD, which was provided by IMS data. The applicant predicts that the market share uptake rates for vortioxetine will mirror that of agomelatine (most recent new entrant onto the market) from year 1 (0.2%), year 2 (0.9%), year 3 (1.6%), year 4 (1.8%) and year 5 (1.7%). Based on these uptake rates

the applicant predicts that the number of DDDs used of vortioxetine from year 1 to 5 will be 230,306, 1,134,080, 2,206,209, 2,715,968, and 2,806,898.

Based on the predicted number of DDDs used of vortioxetine, the applicant estimated the gross cost of vortioxetine to the HSE by multiplying the total number of DDDs of vortioxetine by the average cost per DDD to the HSE of vortioxetine. The predicted gross medicine acquisition costs for vortioxetine for year 1 to year 5 were; €339,044, €1,669,528, €3,247,855, €3,998,293 and €4,132,155.

The applicant predicts that the displaced treatments will constitute mainly those in the 2nd and 3rd line setting (approximately 95% in total, covering agomelatine, sertraline, duloxetine and venlafaxine), with the remaining 5% being displaced treatments in the first line setting, mainly citalopram and escitalopram.

The net drug-budget impact of vortioxetine is estimated for year 1 to year 5 as €259,495, €1,277,810, €2,485,818, €3,060,183 and €3,162,637. The cumulative net cost of vortioxetine over 5 years was estimated to be €10,245,944.

5. Conclusion

Following NCPE assessment of the company submission, vortioxetine (Brintellix®) is not considered cost-effective for the treatment of major depressive episodes in adults and therefore is not recommended for reimbursement.