Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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vortioxetine 5mg, 10mg, 20mg film-coated tablet (Brintellix®)

SMC No. (1158/16)

Lundbeck Ltd.

10 June 2016

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

vortioxetine 5mg, 10mg, 20mg film-coated tablet (Brintellix®) is accepted for restricted use within NHS Scotland.

Indication under review: the treatment of major depressive episodes in adults.

SMC restriction: patients who have experienced an inadequate response (either due to lack of adequate efficacy and/or safety concerns/intolerability) to two or more previous antidepressants.

In two phase III, randomised, double-blind studies in adults with major depressive disorder, vortioxetine was non-inferior to two alternative antidepressants at reducing the Montgomery-Åsberg Depression Rating Scale (MADRS) total score from baseline to week 8.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

The treatment of major depressive episodes in adults.

Dosing Information

In adults <65 years of age, 10mg taken orally once daily. Depending on individual patient response, the dose may be increased to a maximum of 20mg once daily or decreased to a minimum of 5mg once daily.

In adults ≥65 years of age, the lowest effective dose of 5mg once daily should always be used as the starting dose. Caution is advised when treating patients ≥65 years of age with doses higher than 10mg vortioxetine once daily for which data are limited.

After the depressive symptoms resolve, treatment for at least six months is recommended for consolidation of the antidepressive response. Patients can abruptly stop taking the medicinal product without the need for a gradual reduction in dose.

Product availability date

01 September 2015

Summary of evidence on comparative efficacy

Vortioxetine is an antidepressant with multimodal activity, namely direct modulation of serotonergic receptor activity and inhibition of the serotonin (5-HT) transporter, leading to modulation of neurotransmission in predominantly the serotonin system, but probably also the norepinephrine, dopamine, histamine, acetylcholine, GABA and glutamate systems.[1]

The submitting company has requested that SMC considers vortioxetine when positioned for use in the treatment of adult patients with major depressive episodes (MDE) who have experienced an inadequate response (either due to lack of adequate efficacy and/or safety concerns/intolerability) to two or more previous antidepressants.

REVIVE was a phase III, randomised, multicentre, double-blind, non-inferiority study to compare the efficacy and tolerability of vortioxetine versus agomelatine in adults aged 18 to 75 years old suffering from major depressive disorder (MDD) with inadequate response to monotherapy with a selective serotonin reuptake inhibitor (SSRI) or serotonin-noradrenaline reuptake inhibitor (SNRI).[2,3,4] The study recruited patients with an inadequate response to at least six weeks' monotherapy with citalopram, escitalopram, paroxetine, sertraline, duloxetine or venlafaxine for the treatment of a single episode or recurrent MDD based on the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition Text Revision (DSM-IV-TR) criteria, with a current MDE of <12 months duration, a Montgomery-Åsberg Depression Rating Scale (MADRS) total score ≥22 and item 1 (apparent sadness) score of ≥3 at the screening and baseline visits. Patients tapered their current treatment to the minimum therapeutic dose during the week prior to baseline and were randomised equally to switch to either vortioxetine (10 to 20mg/day) or agomelatine (25 to 50mg/day) encapsulated tablets taken orally once-daily, preferably at bedtime, for a duration of 12 weeks. Patients started treatment at the lower dose, which was optimised using a flexible-dose design for the first four weeks of treatment, after which the dose was fixed.

The primary efficacy outcome was the change in MADRS total score from baseline to week 8. The MADRS total score ranges from 0 to 60, with a higher score indicating more severe symptoms. Assessment of non-inferiority was performed in the full analysis set (all randomised patients who took at least one dose of study drug and had a valid baseline assessment and at least one valid post-baseline assessment). If the upper bound of the two-sided 95% confidence interval (CI) of the difference between treatment groups in MADRS total score at week 8 did not exceed +2 MADRS points for vortioxetine versus agomelatine, then non-inferiority was demonstrated. The mean (standard error [SE]) change in MADRS total score from baseline to week 8 was -16.5 (0.48) points in the vortioxetine group and -14.4 (0.51) points in the agomelatine group. Non-inferiority was established with a mean (SE) difference of -2.2 (0.7) points (95% CI: -3.5 to -0.8). As the 95% CI excluded zero, vortioxetine was also considered to be superior to agomelatine (p=0.0018). The results were confirmed by sensitivity analyses, and similar results were also obtained at week 12 (secondary efficacy analysis). A significantly higher proportion of patients responded to treatment (≥50% decrease in the MADRS total score from baseline) and were in remission (MADRS total score ≤10) with vortioxetine at weeks 8 and 12 (assessed as secondary efficacy outcomes), compared with agomelatine. Results are presented in table 1.

Table 1: REVIVE response and remission rates at weeks 8 and 12 (full analysis set)[3,4]

	Vortioxetine (n=252)	**Agomelatine** (n=241)	**Odds ratio (95% confidence interval)**	**p-value**
Week 8				
Response	62%	47%	1.8 (1.3 to 2.6)	0.001
Remission	41%	30%	1.7 (1.2 to 2.5)	0.005
Week 12				
Response	70%	56%	1.8 (1.3 to 2.6)	0.001
Remission	55%	39%	2.0 (1.4 to 2.9)	0.000

Change in the Hamilton Anxiety Rating Scale (HAM-A) total score was assessed as a secondary outcome. The HAM-A total score ranges from 0 to 56, with a higher score indicating greater anxiety. From baseline to week 8, there was a significantly greater reduction in the score for the vortioxetine group with a mean (SE) change of -11.7 (0.4) points, versus the agomelatine group with -9.8 (0.4) points; mean (SE) difference of -1.9 (0.6) points (95% CI: -3.0 to -0.8), p=0.0008. Similar results were obtained at week 12. Significantly greater improvements were also seen in the Clinical Global Impression-Severity of Illness (CGI-S) score and Clinical Global Impression-Global Improvement (CGI-I) score from baseline to weeks 8 and 12 for the vortioxetine group versus the agomelatine group (secondary outcomes). Vortioxetine was also found to have favourable effects on quality of life as demonstrated by significantly greater improvements in the Sheehan Disability Scale (SDS) total score, EuroQol quality of life-5 Dimensions (EQ-5D) overall health state score and work limitation questionnaire (WLQ) global productivity index, compared with agomelatine.

SOLUTION was a phase III, randomised, multicentre, double-blind, non-inferiority study to compare the efficacy, safety and tolerability of vortioxetine versus venlafaxine extended-release (XR) in adults with MDD.[5,6] The study recruited patients aged 18 to 65 years old with a primary diagnosis of recurrent MDD (based on DSM-IV-TR criteria), a current MDE of at least three months duration, MADRS total score ≥26 and CGI-S score ≥4 at screening and baseline. Patients considered by the investigator to be resistant to two adequate antidepressants of at least six weeks' duration were excluded from the study. Patients were randomised equally to treatment with vortioxetine (10mg/day) or venlafaxine XR (75mg/day for four days then 150mg/day) taken orally, preferably in the morning, for eight weeks, followed by a one-week tapering phase in which vortioxetine was switched to placebo and the venlafaxine dose was reduced to 75mg/day.

The primary efficacy outcome was the change in MADRS total score from baseline to week 8. Assessment of non-inferiority was performed in the full analysis set (as defined for REVIVE). If the upper bound of the two-sided 95% CI of the difference between treatment groups in MADRS total score at week 8 was <2.5 MADRS points for vortioxetine versus venlafaxine XR, then non-inferiority was established. The mean (SE) change in MADRS total score from baseline to week 8 was -19.4 (0.7) points in the vortioxetine group and -18.2 (0.7) points in the venlafaxine XR group. Non-inferiority was established with a mean (SE) difference of -1.2 (0.9) points (95% CI: -3.0 to 0.6), p=0.20. Sensitivity analyses confirmed the results.

A post-hoc efficacy analysis was conducted on all randomised patients who took at least one dose of study drug (as a result of there being significantly more patients treated with venlafaxine XR who withdrew from the study and had no valid post-baseline assessment); a zero change from baseline was imputed for these patients. The mean (SE) change in MADRS total score from baseline to week 8 was -19.2 (0.7) points in the vortioxetine group (n=211) and -17.3 (0.7) points in the venlafaxine XR group (n=226), with a mean (SE) difference of -1.9 (0.9) points (95% CI: -3.76 to -0.04), p=0.0452.

Secondary outcome analyses demonstrated a numerical (but not statistical) advantage for vortioxetine over venlafaxine XR for response and remission rates (see table 2), and change in HAM-A total score, CGI-S score and CGI-I score.

Table 2: SOLUTION response and remission rates at week 8 (full analysis set)[5,6]

	Vortioxetine (n=209)	**Venlafaxine XR** (n=215)	**Odds ratio (95% confidence interval)**	**p-value**
Response	66%	61%	1.2 (0.8 to 1.9)	0.272
Remission	43%	41%	1.1 (0.7 to 1.6)	0.731

Vortioxetine also demonstrated slightly greater numerical improvements in the SDS total score and similar results measured by the Quality of Life, Enjoyment and Satisfaction Questionnaire (Q-LES-Q) compared with venlafaxine XR.

Summary of evidence on comparative safety

In REVIVE, treatment-emergent adverse events were reported in 54% (137/253) and 52% (127/242) of patients in the vortioxetine and agomelatine groups, respectively, of which 1.2% (3/253) and 1.6% (4/242) were considered to be serious. Treatment discontinuation as a result of any treatment-emergent adverse events occurred less frequently in the vortioxetine group (5.5%) versus the agomelatine group (8.3%). The most commonly reported adverse events in the both groups were nausea (16% in the vortioxetine group versus 9.1% in the agomelatine group), headache (10% versus 13%), dizziness (7.1% versus 12%), and somnolence (4.0% versus 7.9%). Sleep-related treatment-emergent adverse events (including insomnia, somnolence, initial/middle/terminal insomnia and sleep disorder) were reported in 11% of patients in both groups. Sexual dysfunction as a result of treatment-emergent adverse events was reported by one patient (0.4%) taking vortioxetine. No patients reported suicidal behaviour during the study, and self-injurious ideation occurred in one patient in the agomelatine group. Both treatment groups demonstrated an improvement in the MADRS item 10 suicidal thoughts score and a significantly greater effect was seen in the vortioxetine group from week four onwards ($p<0.05$).[3]

In SOLUTION, treatment-emergent adverse events were reported in 59% (125/211) and 68% (153/226) of patients in the vortioxetine and venlafaxine XR groups, respectively, of which 0.9% (2/211) and 3.5% (8/226) were considered to be serious. Treatment discontinuation as a result of any treatment-emergent adverse events occurred less frequently in the vortioxetine group (6.6%) versus

the venlafaxine XR group (14%). The most commonly reported treatment-emergent adverse events in vortioxetine group were nausea (reported by 24% in both groups), dizziness (8.1% in the vortioxetine group versus 13% in the venlafaxine XR group), headache (8.1% versus 6.6%), and dry mouth (5.7% versus 11%). There was a low incidence of suicide-related treatment-emergent adverse events in both groups (1.4% in the vortioxetine group and 1.8% in the venlafaxine XR group), and both demonstrated an improvement in MADRS item 10 (suicidal thoughts) score.[5]

Summary of clinical effectiveness issues

Depression tends to be a chronic disorder that is characterised by frequent relapse and recurrence. The condition can significantly impair an individual's ability to manage everyday responsibilities and in some cases may lead to suicide.[2] MDD is the most widespread mood disorder and despite the range of antidepressants currently available, the European Medicines Agency (EMA) considers there is a need for new products that demonstrate improved efficacy and safety.[2,7] Current UK guidelines recommend first-line pharmacological therapy with an antidepressant, normally an SSRI; second-line therapy with a different SSRI or a better tolerated newer-generation antidepressant; and third-line therapy with an antidepressant of a different pharmacological class that may be less well tolerated, eg venlafaxine, a tricyclic antidepressant (TCA) or a monoamine-oxidase inhibitor (MAOI). Dosulepin is not recommended.[8]

The submitting company has requested that SMC considers vortioxetine when positioned for use in the treatment of adult patients with MDE who have experienced an inadequate response (either due to lack of adequate efficacy and/or safety concerns/intolerability) to two or more previous antidepressants. Based on this positioning, clinical experts consulted by SMC consider that vortioxetine is most likely to displace the use of venlafaxine, mirtazapine or duloxetine.

REVIVE demonstrated that vortioxetine was non-inferior (and also statistically superior) to agomelatine in reducing the MADRS total score. Both scores improved by over 50%, which is considered clinically relevant by the EMA.[7] By week 12, 70% of patients treated with vortioxetine responded to treatment and 55% were considered to be in remission. The study included agomelatine as the active-comparator arm, which is not considered a relevant comparator in Scotland due to SMC not recommended advice. In addition, the study population does not represent the selective positioning proposed by the submitting company.

The Committee for Medicinal Products for Human Use (CHMP) raised concerns over the definition of the patient population in the REVIVE study as patients who 'responded inadequately' to SSRI/SNRI monotherapy. The assumed inadequate response was based on the mean MADRS total score at baseline/randomisation without any evidence of the severity of depression when the first SSRI/SNRI was initiated. In addition, data on response and patient compliance to the SSRI/SNRI were collected retrospectively, and it could not be established if partial responders were included in the study population due to the absence of data for the lead-in period. The reasons for inadequate response (which could potentially have included a lack of patient compliance) were also not identified in the study. The CHMP concluded that the efficacy results of the study could only be considered as supportive for that patient population and could not claim efficacy of vortioxetine in treatment-resistant patients, or in patients with MDD who responded inadequately to SSRI/SNRI monotherapy, as the patient population was only retrospectively defined.[2]

SOLUTION demonstrated vortioxetine was non-inferior to venlafaxine XR in reducing the MADRS total score, and the post-hoc analysis demonstrated a statistically significant advantage for vortioxetine. Again, a clinically relevant improvement of over 50% was seen in both treatment groups.[7] At week 8, 66% of patients treated with vortioxetine responded to treatment and 43% were considered to be in

remission. The study only included the extended-release formulation of venlafaxine as the active-comparator arm. Patients who were resistant to two adequate antidepressants of at least six weeks' duration were excluded and therefore the study population may not wholly represent the selective positioning proposed by the submitting company.

Patients with co-morbid disorders (other than general/social anxiety disorder), those at significant risk of suicide and those receiving psychotherapy were excluded from the studies which may affect the generalisability of the results to the Scottish population; however, the exclusion criteria were considered acceptable by the EMA. Both studies were conducted in a specialist psychiatric setting and adjunctive cognitive or behavioural therapy was prohibited. In addition, SOLUTION was conducted in Asian patients only, but based on pharmacokinetic data, the EMA considered that there were no clinically meaningful changes in vortioxetine exposure related to race or ethnicity. Both studies evaluated the efficacy of vortioxetine at a dose of 10mg to 20mg daily, therefore comparative efficacy of the licensed 5mg daily dose is unclear. As a result of the relatively short duration of the studies, data on long-term efficacy and safety are lacking.

A published meta-regression analysis[9] (funded by the submitting company) indirectly compared vortioxetine with agomelatine, desvenlafaxine, duloxetine, escitalopram, sertraline, venlafaxine immediate-release (IR), venlafaxine XR and vilazodone. Of these treatments, duloxetine, venlafaxine IR and venlafaxine XR are considered relevant comparators for the selective positioning sought by the submitting company as these treatments are likely to be used third-line in Scotland as indicated by clinical experts. Desvenlafaxine and vilazodone are not marketed in the UK. The primary analyses included study treatment and placebo arms from randomised, double-blind, placebo-controlled registration studies conducted in adults with MDD. Data from active reference arms were excluded. The included studies were required to have a primary efficacy outcome which assessed the MADRS or Hamilton Depression Rating Scale (HAM-D) scores after two months of antidepressant treatment. Efficacy (estimates of treatment effect of standardised mean difference in change in MADRS/HAM-D score from baseline to two months) and tolerability (withdrawal rate due to adverse events during the first two months of treatment) were the two main outcomes assessed. The results demonstrated no difference in efficacy between vortioxetine and the relevant comparators. Vortioxetine was, however, found to have a favourable tolerability profile compared with venlafaxine IR/XR. Response (≥50% reduction in score) and remission (defined by study sources) were conducted as additional sensitivity analyses; however, due to a large number of studies with missing data for these outcomes (in some cases as a result of failed studies), analyses for these outcomes were considered weak. The results demonstrated no significant differences between treatments. Heterogeneity was apparent across the studies in a number of areas including patient population, primary efficacy score measured (MADRS or HAM-D) and duration of treatment (range from six to nine weeks). As the patient populations of the included studies were not restricted to third-line antidepressant use in line with the selective population for this submission, the applicability of the results has some limitations.

An indirect treatment comparison (ITC) comprising three studies compared vortioxetine with agomelatine, venlafaxine XR, sertraline and bupropion slow-release (SR). Only venlafaxine XR is considered a relevant comparator. Bupropion SR is not licensed in the UK for the treatment of depression. The outcomes reported were rate of response, remission and withdrawal due to adverse events, assessed using the Bucher method. Response was defined as a ≥50% reduction in symptoms as measured by a depression symptom scale (eg HAM-D17, MADRS or Quick Inventory of Depressive Symptomatology–Self-Report [QIDS-SR16]). Remission was defined as a HAM-D17 score ≤7 or a MADRS score ≤10. The results demonstrated that vortioxetine had a numerically higher remission rate although this was not statistically significant. Response rate and withdrawal due to adverse events were significantly improved with vortioxetine compared with venlafaxine XR. The relevance of the ITC was limited as it was only conducted in those patients requiring second-line therapy, which does not correspond with the selective positioning for vortioxetine. The use of the

Bucher method means no adjustment was made for heterogeneity, which is a limitation of the analysis.

No direct or indirect evidence was presented to compare vortioxetine with mirtazapine.

Vortioxetine has the advantage that treatment can be stopped abruptly without the need for a gradual reduction in dose and it would provide an alternative antidepressant option with a different mode of action for the treatment of MDEs.[1] While short-term data suggests that vortioxetine may be associated with a lower probability of stopping treatment and fewer adverse effects compared to alternative antidepressants, longer term data showing any potential advantage in terms of adverse event profile are unavailable.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis which compared vortioxetine against a range of comparators in adult patients with an MDE who have experienced an inadequate response (either due to lack of adequate efficacy and/or safety concerns/tolerability) to two or more previous antidepressants. The comparators included venlafaxine IR, venlafaxine XR, sertraline and agomelatine, and the company considered the venlafaxine medicines to be of greatest relevance.

The company used a decision tree with a Markov component to evaluate the cost-effectiveness of vortioxetine in the patient population over a total time horizon of 24 months. The decision tree described the possible pathways patients may follow on entry to the model and included: an acute phase of treatment for 8 weeks (months 0-2), a maintenance phase of 6-22 months (months 2-8/24), and a recovery phase (months 8-24 in the case of a 6 month maintenance phase). It is also worth noting that the model did not consider a recovery phase where the maintenance phase was extended to 22 months, given the total modeled horizon of 2 years. At 8 weeks, patients were able to take one of three efficacy pathways: remission, response but no remission, and no response. Patients who were initially classified as responders at 8 weeks were re-assessed at 12 weeks and could remain in response, or be classified as in remission or no response. Patients could also discontinue treatment because of adverse events. The response to treatment and adverse events determined how long patients would remain in the decision tree before transferring to the Markov structure, which captured patients switching to fourth and later lines of treatment.

The sources of the clinical data used in the economic model included the REVIVE study which informed the remission and no response rate for vortioxetine and agomelatine. The remission and no response rate for venlafaxine and sertraline were assumed to be the same as vortioxetine based on non-significant differences from the ITC or assumption. It is also worth noting that the remission and no response rates were adjusted for third line use by applying the proportional reduction in efficacy observed in the STAR*D study between 2nd and 3rd line treatments. The STAR*D study evaluated the acute and longer-term outcomes of treatment sequences and concluded that additional treatment steps reduced the remission rates and increased relapse rates.[10] Discontinuation due to short term adverse events was also informed by the rates observed in the REVIVE study or the results of the ITC. Short and long term adverse events rates were generated from relevant clinical studies.

The utility values for remission, response without remission, no response and relapse were taken from EQ-5D data which were collected through the REVIVE study. Disutilities for adverse events were taken from published studies.

Medicines costs were included in the analysis as were costs associated with liver function tests, disease monitoring and management, and adverse events.

The results indicated that the incremental cost-effectiveness ratios (ICER) for vortioxetine versus venlafaxine IR and XR were £1,997 and £1,351 per quality adjusted life year (QALY) gained respectively. These results were based on an incremental cost of £36 and £24 and an incremental QALY gain of 0.018 and 0.018 respectively. In terms of the comparison versus sertraline and agomelatine, the ICER versus sertraline was £2,868 and vortioxetine dominated agomelatine (ie was more effective and less costly). These results were based on an incremental cost of £45 and -£293 and an incremental QALY gain of 0.016 and 0.047 respectively. The company also presented the base case results as an incremental analysis where venlafaxine (IR and XR), and agomelatine were dominated by sertraline. The ICER for vortioxetine versus sertraline was £2,868 based on the same incremental costs and QALYs as reported above.

The economic analysis was most sensitive to changing efficacy assumptions:

- When the response/no remission rate at 8 weeks was increased from 37.07% to 46.71% for venlafaxine IR and sertraline, vortioxetine was dominated by the comparators.
- Increasing remission rate at 12 weeks from 59.52% to 68.89% for venlafaxine IR and sertraline increased the ICER to £12,571 and £24,489 respectively.
- Increasing the response/no remission rate at 12 weeks from 32.14% to 41.56% for sertraline increased the ICER to £16,852 versus sertraline.

The economic analysis also demonstrated sensitivity to the maintenance phase length as when this was increased to 22 months the ICERs were £14,509, £12,649, and £17,259 versus venlafaxine IR, venlafaxine XR and sertraline respectively. When a 22 month maintenance phase length was combined with delivering treatment in secondary care, the ICER increased to £12,270, £10,410, and £14,423 versus venlafaxine IR, venlafaxine XR and sertraline respectively. It is worth noting that in all sensitivity analyses referenced above agomelatine was dominated by vortioxetine.

The main weaknesses were

- The company did not initially include all relevant comparators in the analysis as duloxetine and mirtazapine were identified as treatment options by SMC clinical experts. The company subsequently provided sensitivity analyses versus these medicines which generated a base case ICER versus mirtazapine of £4,962. When the maintenance phase length was extended to 22 months, the ICER versus mirtazapine increased to £25,147, and when the maintenance phase length was extended to 22 months and combined with treatment delivered in secondary care, the ICER versus mirtazapine increased to £21,069. Versus duloxetine, vortioxetine was dominant in the base case, and the ICER increased to £12,056 when the maintenance phase length was extended to 22 months. However, the evidence base which supported the analyses versus mirtazapine and duloxetine had a number of limitations.
- A limitation with the analysis was that it was difficult to determine which variables were generating the QALY gain for vortioxetine given the non-significant differences in the ITC, but clarification from the company indicated that the gains were driven by tolerability differences. However, some of these adverse event rates were not derived from the ITC and were instead taken from unadjusted data sources. The company presented threshold-based sensitivity analysis to show the levels of reduction in adverse events for the comparators that would be required for the cost per QALY to reach £20k or £30k. The analysis suggested that for adverse events where direct or indirect data were not available, the unadjusted comparator rates would have to reduce by approximately 70% and upwards for the vortioxetine ICERs to be above these thresholds.
- The ITC which established the comparative efficacy of vortioxetine versus the comparators was associated with a number of weaknesses, as noted above.

Despite the above uncertainties the economic case has been demonstrated.

Summary of patient and public involvement

The following information reflects the views of the specified patient group.

- A submission was received from Action on Depression, which is a registered charity.
- The patient group has not received any pharmaceutical company funding in the past two years.
- Depression affects all aspects of patients' day to day lives. Feelings of hopelessness, trouble sleeping, lack of motivation and low energy are all common. This can impact on ability to interact, maintain employment, undertake daily activities and have healthy relationships. Patients may also have low self esteem and a sense of worthlessness.
- Those with depression can have difficulty distinguishing what is helping their condition, especially if they are taking medication alongside other forms of treatment or therapy. The benefits of antidepressant medicines were highlighted, including "feeling normal", improved sleep regulation and being more able to go out.
- New medicines for depression are expected to improve quality of life for patients including increased ability to cope with everyday life, improvement in mood and a reduction in anxiety. Side-effect profile and stigma associated with taking medication for depression were noted as potential disadvantages of antidepressant treatment in general.

Additional information: guidelines and protocols

In 2010, the National Collaborating Centre for Mental Health published an update to the national clinical practice guideline 90: Depression – the NICE guideline on the treatment and management of depression in adults.[8] The guideline recommends discussing antidepressant treatment options with the patient including choice, adverse events, discontinuation symptoms and potential interactions, as well as their perception of the efficacy and tolerability of any antidepressants previously taken. When an antidepressant is to be prescribed, it should normally be a generic SSRI as they are considered to be equally effective as other antidepressants with a favourable risk–benefit ratio. If there is no improvement after two to four weeks with the first antidepressant, prescribers should ensure the drug has been taken regularly at the prescribed dose. If there is an absent or minimal response after three to four weeks of treatment at a therapeutic dose, the level of support should be increased and an increase in dose or switch to another antidepressant should be considered. If some improvement is seen by four weeks, treatment should be continued for another two to four weeks. Switching to another antidepressant should be considered if response remains inadequate, there are side effects or the person prefers to change treatment. The evidence for the relative advantage of switching either within or between antidepressant classes is weak. If switching, initially a different SSRI or a better tolerated newer-generation antidepressant should be considered, and subsequently a switch to an antidepressant of a different pharmacological class that may be less well tolerated, for example venlafaxine, a TCA or an MAOI. Dosulepin is not recommended.

In 2015, the British Association for Psychopharmacology published evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 2008 guidelines.[11] The guidelines recommend that the choice of antidepressant should match the individual needs of the patient as much as possible, taking into account short- and long-term effects. Antidepressants that are better

tolerated and safer in overdose should be selected. Most evidence is for the SSRIs which, together with other newer antidepressants, are first-line choices. Older TCAs and MAOIs and should generally be reserved for use after failure of first-line drug treatment (MAOIs should only be initiated by clinicians with expertise in the treatment of mood disorders). Clomipramine, venlafaxine, escitalopram, sertraline, amitriptyline, or mirtazapine should be considered for severely ill patients. Antidepressants should be continued for at least four weeks before switching treatment due to a lack of efficacy. Treatment should be continued for a further two to four weeks if there is at least some improvement. If there is no improvement, consider increasing the dose or switching to an alternative antidepressant, either within- or between-antidepressant class initially. Switching to a different antidepressant class should be considered after more than one failure with a specific class. Consider switching to venlafaxine after more than one SSRI failure and consider preferentially those antidepressants with some evidence of slightly higher efficacy (i.e. clomipramine, venlafaxine [≥150mg], escitalopram [20mg], sertraline, amitriptyline or mirtazapine).

Both guidelines predate the availability of vortioxetine.

Additional information: comparators

Venlafaxine, mirtazapine, duloxetine.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Vortioxetine	**Orally, 5mg to 20mg daily**	**360**
Venlafaxine extended-release	Orally, 75mg to 375mg daily	136 to 635
Duloxetine	Orally, 60mg daily	227
Venlafaxine standard-release	Orally, 75mg to 375mg daily	20 to 99
Mirtazapine	Orally, 15mg to 45mg daily	24 to 27

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 08/03/16.

Additional information: budget impact

The company estimated there would be 28,273 patients eligible for treatment with vortioxetine in year 1 and 28,613 patients in year 5, to which confidential estimates of treatment uptake were applied.

The gross impact on the medicines budget was estimated to be £83k in year 1 and £422k in year 5. As medicines were assumed to be displaced, the net medicines budget impact was estimated to be £70k in year 1 and £352k in year 5.

*Other data were also assessed but remain commercially confidential.**

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

1. European Medicines Agency. Assessment report for an initial marketing authorisation application for vortioxetine (Brintellix). EMA/699150/2013. Procedure No. EMEA/H/C/00271724. October 2013.

2. Lundbeck Limited. Brintellix® tablets 5, 10 and 20mg. Summary of product characteristics. Date of revision of the text: 17 June 2015

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This assessment is based on data submitted by the applicant company up to and including 13 May 2016.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Policy_Statements*

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.