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CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

VORTIOXETINE HYDROBROMIDE (TRINTELLIX)

(Lundbeck Canada Inc.)

Indication: The treatment of major depressive disorder in adults.

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Abbreviations

AE	adverse event
CANMAT	Canadian Network for Mood and Anxiety Treatments
CrI	credible interval
DDD	defined daily dose
EQ-5D	EuroQol 5-Dimensions
ICUR	incremental cost-utility ratio
MDD	major depressive disorder
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
OR	odds ratio
QALY	quality-adjusted life-year
RCT	randomized controlled trial
SNRI	serotonin-noradrenaline reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
STAR*D	Sequenced Treatment Alternative to Relieve Depression

Table 1: Summary of the Manufacturer's Economic Submission

Drug product	Vortioxetine (Trintellix)
Study question	What is the incremental cost-effectiveness ratio for vortioxetine compared with other antidepressants for the initial treatment of adults with major depressive disorder (MDD)?
Type of economic evaluation	Cost-utility analysis
Target population	MDD patients on first-line therapy
Treatment	Vortioxetine
Outcome	Quality-adjusted life-years (QALYs)
Comparators	**SNRIs** • duloxetine, venlafaxine **SSRIs** • citalopram, escitalopram, fluoxetine, paroxetine, sertraline **Others** • bupropion, mirtazapine
Perspective	Canadian publicly funded health care payer
Time horizon	One-year
Results for base case	In a sequential analysis: • The ICUR for duloxetine versus bupropion: $50,025 per QALY • The ICUR for vortioxetine versus duloxetine: $89,785 per QALY • Citalopram, escitalopram, fluoxetine, fluvoxamine, mirtazapine, paroxetine, sertraline, and venlafaxine were dominated by bupropion due to higher costs and fewer QALYs.
Key limitations	CADTH identified the following key limitations: • The comparative treatment effects of vortioxetine with relevant comparators are uncertain given the limitations of the manufacturer's submitted NMA as identified by CADTH clinical reviewers. • Response rates were inappropriately excluded from the model. • The relapse utility was assumed to be equal to patients not achieving remission, favouring vortioxetine. • Unadjusted short- and long-term AE probabilities were applied in the model and it was uncertain if these studies represent the expected frequency of AEs. • An average utility decrement was inappropriately applied to AEs in the absence of data. • Treatment costs were not calculated appropriately according to utilization in Canada. • Recovery health-state costs were not applied in the model; however, CANMAT guidelines recommend extended treatment for patients achieving remission. The clinical expert confirmed that at-risk patients would likely incur follow-up visits as part of routine care during recovery. • A relevant subsequent augmentation treatment (quetiapine) was not included. • The impact of subsequent treatment sequencing is uncertain.
CADTH estimate(s)	• CADTH addressed these limitations where possible by altering the treatment augmentation, applying unstratified dosing ORs from the NMA, altering the relapse utility, modifying long-term AE probabilities, calculating appropriate treatment costs, and modifying subsequent treatment sequencing. • Based on CADTH's base-case reanalyses, vortioxetine was dominated by duloxetine and escitalopram.

AE = adverse event; CANMAT: Canadian Network for Mood and Anxiety Treatments; ICUR = incremental cost-utility ratio; MDD = major depressive disorder; NMA = network meta-analysis; OR = odds ratio; QALY = quality-adjusted life-year.

Drug	Vortioxetine (Trintellix)
Indication	Treatment of major depressive disorder in adults
Reimbursement request	As per indication
Dosage form(s)	5 mg, 10 mg, 15 mg, and 20 mg tablets
NOC fate	October 22, 2014
Manufacturer	Lundbeck Canada Inc.

NOC = Notice of Compliance.

Executive Summary

Background

Vortioxetine (Trintellix) is a serotonin reuptake inhibitor indicated for the treatment of MDD in adults.[1] The recommended starting dosage is 10 mg per day for adults and the dosage may be increased to a daily maximum of 20 mg or reduced to 5 mg daily for individuals unable to tolerate higher doses. The recommended starting dosage for adults 65 years of age and older is 5 mg daily, and caution is advised in treating elderly patients with doses greater than 10 mg.[1] The manufacturer submitted a price of $2.81 per 5 mg, $2.95 per 10 mg, and $3.20 per 20 mg tablet.[2] CADTH previously reviewed vortioxetine for the treatment of MDD in 2015, but the submission was voluntarily withdrawn by the manufacturer.[3]

The manufacturer submitted a cost-utility analysis considering vortioxetine versus other antidepressants for the treatment of MDD episodes as a first-line treatment[2] from the perspective of a Canadian publicly funded health care payer over a one-year time horizon. Comparators included serotonin-noradrenaline reuptake inhibitors (duloxetine and venlafaxine), selective serotonin reuptake inhibitors (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline), and two treatments with different mechanisms of action (bupropion and mirtazapine). The model consisted of a combined decision tree and Markov model in which a hypothetical cohort of treatment-naive patients with MDD start in the model in the decision tree and progress to subsequent lines of treatment in the model. Patients transition to subsequent treatment due to relapses, short- and long-term adverse events (AEs), or lack of treatment efficacy. The manufacturer submitted a network meta-analysis (NMA) of the comparative efficacy and rate of withdrawal due to AEs between vortioxetine and comparators, based on a recent publication by Cipriani et al.,[4] which included 522 randomized controlled trials. The manufacturer stratified treatments according to dose and transformed the results by applying the odds ratio (OR) to placebo values for remission rates and discontinuation due to AEs. Discontinuation for first-line treatment and short- and long-term AEs were assumed to occur over the first two-month cycle only, with no discontinuation occurring during second- or third-line treatment. Health-state utility values were obtained from the REVIVE study[5] for "baseline depression," "remission," and "no remission" health states. Utility decrements due to AEs were also applied in the model. Health care utilization and costs for health states were based on estimates from clinical experts. Drug acquisition costs for vortioxetine were based on the manufacturer's submitted price and unit drug prices for comparators were obtained from the Ontario Drug Benefit program.[6]

In the manufacturer's base case, vortioxetine was associated with both higher costs and QALYs when compared to all other comparators. Based on the sequential analysis, bupropion is the preferred option if a decision-maker is willing to pay $49,000 per QALY; duloxetine is the preferred option if a decision-maker is willing to pay between $50,000 and $89,000 per QALY; and vortioxetine is preferred if the decision-maker is willing to pay more than $89,000 per QALY.

Summary of Identified Limitations and Key Results

CADTH identified several limitations with the economic model submitted by the manufacturer. The stratification of trials according to dose in the manufacturer's NMA was considered inappropriate by CADTH clinical reviewers given the additional variability introduced into the analysis and the similarity of overall findings to the results reported by Cipriani et al.[4] Additionally, vortioxetine was associated with a similar efficacy and acceptability (i.e., remission and withdrawal frequency) versus the relevant comparators included in the economic model.

The manufacturer included unadjusted rates for AEs to emphasize the safety profile of vortioxetine. The probabilities of AEs for comparator treatments were obtained using patient-perceived reporting of AEs, and the comparability with open-label trials of vortioxetine, which were documented by the study investigators using standardized reporting methods, is uncertain. Additionally, because the frequency of most AEs between comparators was not statistically different, the same rates of AEs were considered for comparator treatments in the CADTH reanalyses.

The manufacturer assumed experiencing a relapse would have the same utility value for patients as failing to achieve remission. However, based on clinical expert feedback and the vortioxetine submission to the National Institute for Health and Care Excellence,[7] CADTH concluded that the utility value for baseline depression would better reflect patient quality of life following a relapse. While multiple AEs were assumed to result in an equal utility decrement based on findings from Sullivan et al.,[8] the vortioxetine submission[7] and Young et al.[9] both indicated these AEs are not expected to have a substantial impact on patient quality of life.

Treatment acquisition costs were incorrectly applied in the model using a weighted average for costs between available treatment strengths and a cost per milligram using the lowest available strength. CADTH recalculated treatment costs based on current utilization in Canada using IQVIA claims data[10] and applied the resulting cost per milligram to the average daily dose of treatments.

Subsequent treatments (i.e., second- and third-line treatments) were included as part of the manufacturer's base-case analysis. However, due to the heterogeneity of MDD patients and a lack of available clinical data, predicting patient treatment algorithms introduced substantial uncertainty into the analyses. To isolate the treatment effect of vortioxetine in the first-line setting, CADTH considered a common treatment sequencing approach for second- and third-line treatments was more appropriate.

Although the clinical expert consulted by CADTH and the Canadian Network for Mood and Anxiety Treatments guidelines[11] identified quetiapine as a relevant augmentation treatment, it was not included in the manufacturer's submission, CADTH therefore revised the economic model to include the corresponding OR for remission and treatment costs in the model.

Conclusions

CADTH addressed some of the limitations described above by adding quetiapine as an augmentation treatment option, applying unstratified dosing ORs from Cipriani et al., altering the relapse utility, modifying long-term AE probabilities, recalculating treatment costs, and applying a common treatment sequencing. Based on CADTH's reanalyses, vortioxetine was dominated by duloxetine and escitalopram, i.e., vortioxetine was associated with greater costs and fewer QALYs. The difference in QALYs between vortioxetine and all comparators was minimal, suggesting similar overall treatment benefit for MDD patients.

The manufacturer's NMA did not consider AEs and there is limited information to suggest clinical differences between vortioxetine and treatment alternatives in regard to clinically important outcomes such as remission and withdrawal due to AEs. As such, vortioxetine is not associated with additional clinical benefits and is not cost-effective at any level of price reduction. At the current daily price of $2.95 to $3.20, price reductions would be required for vortioxetine to be equal in cost to generic duloxetine (67% to 70% price reduction), generic bupropion (80% to 82%), or generic escitalopram (89% to 90%).

The cost-effectiveness of vortioxetine beyond first-line treatment of patients with MDD has not been evaluated by the manufacturer.

Information on the Pharmacoeconomic Submission

Summary of the Manufacturer's Pharmacoeconomic Submission

Overview

The manufacturer submitted a cost-utility analysis based on a combined decision tree and Markov state-transition model for the first-line treatment of MDD episodes in adult patients.[2] The analysis was conducted from the Canadian publicly funded health care payer perspective over a one-year time horizon with a two-month cycle (a half-cycle correction was applied to the Markov model). The base case was a probabilistic analysis of 2,000 iterations with no discount rate applied to costs or benefits. Baseline characteristics of patients were not included in the analysis as the manufacturer assumed individual patient characteristics had no influence on outcomes. General population mortality was also not considered in the model due to the short time horizon and alignment with previous antidepressant models identified in the literature.[12]

The submission assessed vortioxetine versus 10 comparators: serotonin-noradrenaline reuptake inhibitors (SNRIs; duloxetine and venlafaxine), selective serotonin reuptake inhibitors (SSRIs; citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline), bupropion, and mirtazapine. Clinical experts selected comparators based on reimbursement status by the provincial public drug plans and validated them as representative of the current standard of care in Canada.

Decision Tree Structure

A cohort of treatment-naive patients entered the decision tree and received first-line treatment with either vortioxetine or one of the 10 comparators listed above, and subsequently transitioned through a maximum of four nodes as shown in Figure 1. The first node assessed the efficacy of first-line treatment, and patients could transition to one of three outcomes:

- Remission at eight weeks (defined as achieving depression scores in the non-depressed range[13])
- Withdraw from treatment due to short-term AEs at four weeks; these patients subsequently switched to second-line treatment and entered the Markov model in an "uncontrolled depression" health state
- Failure to achieve remission at eight weeks (patients who neither achieved remission nor withdrew due to short-term AEs); these patients subsequently switched to second-line treatment and entered the Markov model in an "uncontrolled depression" health state.

Patients who achieved remission proceeded to the second node could either experience a long-term AE or not, with patients not experiencing an AE transitioning to one of two outcomes (third node):

- Stay on active treatment and proceed to either "recovery" (maintained remission for six consecutive months, did not enter Markov model) or "relapse" (recurrence of depressive symptoms above the non-depressed range within three months)

- Prematurely discontinue treatment, i.e., patients stop taking their first-line treatment after one month and proceed to either “recovery” (maintained remission for six consecutive months, did not enter Markov model) or “relapse” (recurrence of depressive symptoms above the non-depressed range within three months, entered Markov model in an “uncontrolled depression” state).

Patients who achieved remission and experienced a long-term AE transitioned to one of four outcomes:

- Stay on active treatment and proceed to either “recovery” (maintained remission for six consecutive months, did not enter Markov model) or “relapse” (recurrence of depressive symptoms above the non-depressed range within three months, entered Markov model in an “uncontrolled depression” state)
- Receive a treatment adjustment and proceed to either “recovery” (maintained remission for six consecutive months, did not enter Markov model) or “relapse” (recurrence of depressive symptoms above the non-depressed range within three months, entered Markov model in an “uncontrolled depression” state)
- Prematurely discontinue treatment, i.e., patients stop taking their first-line treatment after one month and proceed to either “recovery” (maintained remission for six consecutive months, did not enter Markov model) or “relapse” (recurrence of depressive symptoms above the non-depressed range within three months, entered Markov model in an “uncontrolled depression” state)
- Switch to second-line treatment after two months and enter the Markov model in a “remission” health state.

Markov Model

The Markov model included 13 health states, which were grouped into three types (“uncontrolled depression,” “remission,” and “recovery”), as shown in Figure 2. The manufacturer defined “remission” and “relapse” according to the Sequenced Treatment Alternative to Relieve Depression (STAR*D) trial,[14] which used the 16-item Quick Inventory of Depressive Symptomatology – Self Report. Patients with a score of up to 5 were considered in remission and those with a score of 11 or greater were considered in relapse. Patients entered the model from the decision tree following the first cycle (two months) in either the second-line remission or second-line “uncontrolled depression” health state.

Patients in the second-line “uncontrolled depression” health state could either achieve remission after the first cycle (four months) in the Markov model or transition to the third-line “uncontrolled depression” health state. Patients achieving remission either continue transitioning to subsequent “remission” health states until remission at eight months is achieved, or relapse to third-line “uncontrolled depression.” Similarly, patients in the third-line “uncontrolled depression” health state could either achieve remission on third-line treatment or transition to the “no remission uncontrolled depression” health state (absorbing). If a patient maintains remission after eight months, they subsequently transition to the “recovery” health state (absorbing), in which patients are assumed to be cured of their episode and will not incur further drug or health care costs.

Model Input: Treatment Effectiveness

The manufacturer submitted a NMA, which was informed by the results from Cipriani et al.[4] However, the NMA studies were stratified according to the WHO defined daily dose (DDD). These results were applied in the base-case analysis to inform transition probabilities of all

treatments for “remission” and “withdrawal due to AE” at eight-week nodes of the decision tree. A weighted average according to trial size was used to calculate placebo probabilities using the Cipriani et al.[4] data set. Median ORs from the manufacturer’s NMA were stratified by dose and transformed into probabilities in the base-case analysis. A summary is shown in Table 9.

It was assumed that transition probabilities for patients achieving remission who did not experience a long-term AE or switch treatment due to a long-term AE would have equal outcome probabilities for all first-line treatments, as shown in Table 10. Based on feedback from clinical experts, patients who achieved remission with first-line treatment could prematurely stop treatment without progressing to second-line treatment. The clinical experts estimated that 25% of remitting patients who experienced long-term AEs and 20% of patients without long-term AEs prematurely stopped treatment without switching.

The manufacturer directly applied transition probabilities from Limosin et al.[15] in the decision tree for patients relapsing after previously continuing first-line treatment. The manufacturer assumed that all first-line treatment relapses occurred at the midpoint between “remission” and “recovery” health states (i.e., three months after achieving remission) and the same probability of relapse would apply to both vortioxetine and all comparators in the model. Patients who relapsed after previously achieving remission and prematurely stopped treatment were determined according to the STAR*D trial.[14] Because the STAR*D trial[14] only reported data on relapse rates and median months to relapse, the manufacturer transformed these data into transition probabilities using an exponential decay function.

An exponential decay was also applied to patients who relapsed on second- and third-line treatments in the Markov model, in which the manufacturer assumed the same transition probabilities would apply to all treatments.

Last, remission probabilities for subsequent treatments were informed by the STAR*D trial.[14] Based on feedback from the clinical experts, the manufacturer also included the effect of augmentation therapy for both second- and third-line treatment using atypical antipsychotic drugs (i.e., aripiprazole and lurasidone). For augmentation therapies, the manufacturer applied an OR of 1.84 (95% credible interval [CrI], 1.37 to 2.53), which was informed by Zhou et al.[16]

The manufacturer assumed that all patients would be 100% compliant with treatment.

Model Input: Subsequent Treatment

The manufacturer’s analysis included subsequent treatments in the Markov model following discontinuation of first-line treatment. Transition probabilities were informed by the STAR*D trial,[14] which compared subsequent treatment of bupropion, venlafaxine, and sertraline following failure on citalopram. These probabilities were applied equally between second-line treatments (equal efficacy) and only drug costs were affected. The proportion of atypical antipsychotic drugs used in the base-case analysis was informed by clinical expert opinion, with 80% of patients receiving aripiprazole and 20% lurasidone.

The second- and third-line treatments were grouped according to treatment class (i.e., SNRI, SSRI, etc.) and the distributions were derived based on clinical expert input. The model excluded vortioxetine as a subsequent treatment and patients could not be retreated with the same first-line treatment. In addition, to estimate the proportion of antidepressants according to treatment class in Ontario, projected market shares were based on internal data from the manufacturer.

Model Input: Utilities

The manufacturer used the quality-of-life data provided by the REVIVE study,[5] a randomized controlled trial (RCT) conducted in 14 European countries, and applied a UK preference weight to the EuroQol 5-Dimensions (EQ-5D) questionnaire.[5,9,17] It was assumed by the manufacturer that UK preference weights were equivalent to the Canadian population and the "relapse" and "recovery" health states would have the same utility values as "no remission" and "remission," respectively, as shown in Table 11.

Model Input: Adverse Events

In the decision tree of the manufacturer's model (Figure 1), nine short-term AEs and three long-term AEs were included. Both short- and long-term AEs were assumed to occur over a two-month duration, with the exception of patients withdrawing first-line treatment due to short-term AEs who would only experience the event for one month.

Short-term AE probabilities were obtained from the corresponding Health Canada product monographs (weighted by sample size for multiple dosages), Cochrane reviews,[18-22] or published literature (Baldwin et al.)[23] if data were not available. According to clinical experts, bupropion is typically used to alleviate sexual AEs and it was assumed by the manufacturer that patients had a 0% probability of experiencing this event. Long-term AE probabilities were obtained from Baldwin et al.,[23] Bet et al.,[23] or Weihs et al.,[24] with the assumption that duloxetine would have the same AE probabilities as venlafaxine for sexual dysfunction, insomnia, and weight gain. An overview of short- and long-term AE probabilities is provided in Table 12.

The manufacturer also included costs and utilities associated with both short- and long-term AEs. It was assumed that all AEs could be resolved by visits to a general practitioner and that pharmacological treatment would be given for select AEs (sexual dysfunction and insomnia). Resource utilization associated with general practitioner visits and the proportions of patients receiving pharmacological intervention were informed by clinical expert estimates. In addition, the manufacturer applied utility decrements for both short- and long-term AEs that were sourced from Sullivan et al.[8] and applied over a two-month period (with the exception of first-line patients who withdrew due to AEs and experienced the event for one month). For AEs that were not reported, a weighted average of all utility decrements was applied.

Model Input: Health Care Resource Utilization and Costs

Vortioxetine acquisition costs were supplied by the manufacturer. Drug acquisition costs for comparators were obtained from the Ontario Drug Benefit Formulary[6] and the daily dosing was calculated using a weighted average by sample size of trials from Cipriani et al.[4]

The manufacturer also incorporated health care resource utilization based on clinical expert opinion for both the frequency of use and the proportion of patients expected to use these services per health state. Routine patient monitoring included visits by general practitioners and psychiatrists, laboratory tests, and hospital visits (i.e., inpatient psychiatry hospitalization and emergency room). Unit costs were obtained from the Ontario Case Costing Initiative (2016-2017)[25] and the Ontario Schedule of Benefits for Physician and Laboratory Services.[26,27]

Manufacturer's Base Case

In the base case, the manufacturer reported that vortioxetine was both more expensive (incremental costs from $173 to $372) and more effective (QALYs from 0.0035 to 0.0175) than any of the comparators. Over a one-year time horizon, the incremental cost-utility ratio (ICUR) of each pairwise comparison between vortioxetine and the 10 comparators ranged from $10,700 to $89,785 per QALY, as shown in Table 2. According to the manufacturer's cost-effectiveness acceptability curve, vortioxetine had 11% and 38% chances of being cost-effective at willingness-to-pay thresholds of $50,000 and $100,000 per QALY, respectively. A breakdown of the cost components and the full results, including dominated strategies, are presented in Table 15 and Table 16, respectively.

Based on a full sequential analysis, the manufacturer reported that bupropion, duloxetine, and vortioxetine comprised the cost-effectiveness efficiency frontier and dominated all other treatments. Of these treatments, bupropion had the lowest costs and QALYs, followed by duloxetine and vortioxetine. The resulting sequential ICURs were $50,025 and $89,785 per QALY for bupropion versus duloxetine and duloxetine versus vortioxetine, respectively.

Table 2: Summary of Results of the Manufacturer's Base Case

	Total costs ($)	Total QALYs	ICUR (vortioxetine versus comparator)	ICUR (comparator versus bupropion[a])	Sequential ICUR ($ per QALY)
Non-dominated strategies					
Bupropion	$4,000	0.6886	$79,882	—	—
Duloxetine	$4,058	0.6898	$89,785	$50,025	$50,025
Vortioxetine	$4,371	0.6933	—	$79,882	$89,785

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life year.

[a] Represents the lowest cost option.

Source: Adapted from the manufacturer's pharmacoeconomic submission.[2]

Summary of Manufacturer's Sensitivity Analyses

The manufacturer conducted multiple scenario analyses focused on pairwise comparisons of vortioxetine with all 10 comparators. The scenarios explored included: equal remission probabilities, inclusion of unstratified dose data, alternate long-term AE probabilities, alternate utility and utility decrements, no disease management costs, no AE costs, costs included in "recovery," and a societal perspective. In all scenarios, vortioxetine was associated with the highest total QALYs and costs, except when a societal perspective was adopted, where a reduction in total costs was observed.

As vortioxetine was compared with duloxetine on the efficiency frontier, only results for duloxetine will be presented; however, similar trends were observed for all comparators. The results were most sensitive to the inclusion of unstratified dose data, alternative utility decrements, equal remission probabilities, and inclusion of indirect costs. Based on these scenarios, the ICURs of vortioxetine versus duloxetine ranged from $31,121 (equal remission probabilities) to $167,472 (unstratified dose data) per QALY.

Limitations of Manufacturer's Submission

Uncertain clinical benefit of vortioxetine versus comparators. Based on the findings from Cipriani et al.[4] and the manufacturer-submitted NMA, vortioxetine was associated with a similar efficacy and acceptability (i.e., remission and withdrawal frequency) versus the relevant comparators included in the economic model. Additionally, the findings from the all-trial network in Cipriani et al. highlights a statistically significant difference in remission, favouring duloxetine (OR 1.19; 95% CrI, 1.01 to 1.41).[4] Vortioxetine was only significant when compared to venlafaxine (OR 1.81; 95% CrI, 1.33 to 2.45), fluvoxamine (OR 1.73; 95% CrI, 1.17 to 2.58), and duloxetine (OR 1.52; 95% CrI, 1.13 to 2.05) for withdrawal due to AEs.[4] Therefore, as part of CADTH's scenario analyses, ORs of remission rates at eight weeks and withdrawal due to AEs were adjusted to equal vortioxetine, with the exception of statistically significant results for withdrawal due to AEs, which remained unchanged.

Limitations with the manufacturer's NMA. The NMA conducted by Cipriani et al.[4] had a significant degree of variation in patient characteristics, and the inclusion of older studies posed a risk of affecting efficacy measures due to possible changes in outcome definitions. Although the manufacturer's NMA does leverage both placebo-controlled and head-to-head studies, the analysis further stratifies the evidence base and relies more heavily on biased and dispersed head-to-head comparisons, which was noted by Cipriani et al. The reduction in evidence for each group introduces greater uncertainty to estimates as studies with no information on [redacted]. Furthermore, the results do not vary substantially from the base analysis, as concluded by the manufacturer in the submitted report, raising the question of whether the expanded analyses offer any extra insight aside from adding further uncertainty. The manufacturer's product monograph also indicates that geriatric patients (≥ 65 years of age) initiate treatment with 5 mg dosing and may remain at this dose for maintenance.[1] Considering 12.1% of patients were at least 65 years old in vortioxetine short-term studies, stratifying results according to the WHO DDD may overestimate the benefit (i.e., response and remission) of vortioxetine.[23] Based on these assessments, CADTH considered it more appropriate to use the NMA by Cipriani et al. as part of the CADTH base-case reanalyses for vortioxetine and include the manufacturer's NMA, stratified according to dose, in the scenario analyses.

Response rate. The manufacturer did not incorporate response rates as part of measurement-based care recommended by the Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines[13] and the clinical expert consulted by CADTH. Response rates (defined as a reduction in baseline score of 50% or greater) are commonly used to assess symptom response to treatment and influence decisions regarding subsequent medication adjustments. Specifically, patients who are partial responders (25% to 49% reduction in symptom scores) or non-responders (< 25% reduction) can vary substantially in their treatment pathways.[11] Furthermore, the clinical expert consulted by CADTH emphasized that patients with MDD demonstrating a partial response or a response not in the remission range would typically continue and optimize treatment in addition to receiving add-on therapy (i.e., adjunctive or psychological treatment) prior to switching treatment as assumed in the manufacturer's model. Although the manufacturer included response rates as part of its submitted NMA, the structural limitations in the model prevented CADTH from exploring scenario analyses using this end point. However, response rates were not statistically different between vortioxetine and all comparators and the impact on results may be minimal.

Relapse utility. In the manufacturer's base case, EQ-5D utilities were obtained from the REVIVE study,[5] an RCT comparing the efficacies of vortioxetine and agomelatine. Because utilities were only extended to eight weeks based on the trial duration, it was assumed by the manufacturer that the "no remission" and "remission" utilities would be applicable to "relapse" and "recovery," respectively, in the maintenance phase. CADTH found the "recovery" health state to be a reasonable assumption; however, the "relapse" health state would bias results in favour of vortioxetine when compared with less-efficacious treatment options or treatments with higher rates of long-term AEs. A recent cost-effectiveness publication by Young et al.[9] also derived utilities from the REVIVE trial and provided a utility value for "relapse" (0.56) that assumed this would be the same in patients not achieving a response to treatment during the acute phase. Additionally, a previous submission of vortioxetine to the National Institute for Health and Care Excellence (NICE)[7] indicated that patients entering a "relapse" health state would likely experience a recurrence of moderate-to-severe MDD and a "baseline depression" health-state utility of 0.54 was applied. CADTH considered the review by NICE to be a more appropriate source of utility for "relapse" as patients are likely to experience a complete regression to baseline during a relapse, a position that is supported by clinical expert feedback.

Long-term AE probability uncertainty. Long-term AEs for comparator treatments in the manufacturer's base case were informed by Bet et al.,[28] a naturalistic study conducted in the Netherlands, with patient-perceived AEs collected using the Antidepressant Side Effect Checklist. Using these results, the manufacturer applied equal probabilities according to treatment class (SSRIs or SNRIs), with the assumption that bupropion would not be associated with long-term sexual dysfunction or weight gain. The manufacturer had conducted a targeted literature review to identify alternative long-term AE sources as part of scenario analyses, but the identified studies only included a limited number of relevant comparators (duloxetine, escitalopram, sertraline, venlafaxine) from multiple sources. Only sexual dysfunction was found to be statistically different between SSRIs, venlafaxine, and mirtazapine in univariate analyses, and only mirtazapine was statistically different from SSRIs in multivariate analyses for sexual dysfunction and weight gain. Including stratified AE probabilities for weight gain and insomnia in the model by the manufacturer was therefore considered inappropriate by CADTH. An additional limitation of using this study was that vortioxetine was not included in the analyses and probabilities were informed instead by Baldwin et al.,[23] a regression analysis of placebo-controlled trials and open-label extension studies (52 weeks).

Using the analyses conducted by Baldwin et al. from the open-label studies, the manufacturer derived vortioxetine long-term AE probabilities. The manufacturer used only data for 15 mg to 20 mg vortioxetine doses to be conservative; however, multiple limitations were associated with this publication and its applicability to real-world patients is limited (e.g.,15 mg dosing is not currently marketed in Canada). Only data following the first eight weeks of treatment were used in the analysis, which excludes reported AEs for patients with an extended drug holiday and patients experiencing a continued moderate or severe AEs related to treatment. Additionally, only completers designated by investigators to have benefited from vortioxetine in the short-term trials were included in the open-label extension, suggesting that AE rates were lower than they would be in a clinical population. Lastly, the results of completer rate for the trials, which ranged from 50.1% to 73%, may not capture all long-term AEs associated with vortioxetine treatment due to withdrawal of consent or patients lost to follow-up.[23] These limitations raise uncertainty in the assessment of long-term AE associated with vortioxetine.

A key difference between these studies is the use of patient-perceived AE in Bet et al. compared with the open-label trials, which were documented by the study investigators using the standardized Medical Dictionary for Regulatory Activities. The extent of concurrence between self-reported AE measures with standardized reporting methodologies and whether these represent the expected frequency of long-term AEs is therefore uncertain.

Based on the limitations stated above, CADTH's base-case reanalyses used the lowest reported AE probabilities according to treatment for weight gain and insomnia reported by Bet et al. and applied them to relevant comparators (excluding bupropion). Because the lower long-term AE values from Baldwin et al. were also biased against comparators with similar efficacy to vortioxetine in the manufacturer's model, long-term AE probabilities from the complete open-label period of the vortioxetine trials were used in CADTH base-case reanalyses. Due to the uncertainty associated with these data sources and the incorporation of long-term AEs favouring vortioxetine, CADTH removed long-term AEs from the scenario analysis.

AE utility decrement. The manufacturer-informed AE utility decrements from Sullivan et al.,[8] a cost-utility analysis conducted from the payer perspective in the US that derived age-adjusted EQ-5D utility scores from the Medical Expenditure Panel Survey. Because numerous short- and long-term AEs utility decrements were not reported in the publication, the manufacturer used a weighted average of all AEs as a proxy value for AEs within the model where specific decrements were not available. CADTH did not consider this to be a conservative approach favouring vortioxetine as the weighted average utility decrement (0.085) was nearly twice that of other reported AEs (i.e., sexual dysfunction and diarrhea) and was applied in AEs with substantial discrepancies between vortioxetine and relevant comparators AEs (i.e., dry mouth, sweating, somnolence, and weight gain). A conservative approach taken by the manufacturer's submission in the vortioxetine technology assessment to NICE[7] and the publication by Young et al.[9] involved applying a utility decrement of 0.00 to missing AEs (i.e., dry mouth, sweating, and dizziness). The clinical expert consulted by CADTH also affirmed that most patients would tolerate a dry mouth and it is uncertain if they would experience a utility decrement due to this AE. Additionally, the magnitude of weight gain experienced by MDD patients was unclear, and considering that short-term AEs were assumed to last only two months by the manufacturer, it is difficult to assess the impact on patient quality of life. As a result of the uncertainty associated with assuming a weighted average for missing AEs, CADTH removed the utility decrements for dry mouth, sweating, dizziness, and weight gain in the base-case reanalyses.

As part of CADTH scenario analyses, oral medication AE utility decrements from Matza et al. (2019),[29] a time trade-off study for migraine patients and the general population in the UK, were included for dizziness and dry mouth. Considering MDD is associated with chronic conditions such as migraine, CADTH considered it reasonable to apply these decrements to MDD patients.[13] Additionally, the publications from NICE and Young et al. applied a weight gain decrement of 0.032 in their analyses, which was also included as part of this scenario for AE utility decrements.

Treatment cost calculations. The manufacturer used the WHO DDD to calculate an average daily dose for both vortioxetine and the comparators. If the average daily dose exceeded the uppermost available strength, the cost per milligram in excess using the lowest available strength was applied. In situations where the average daily dose fell between two available strengths, the weighted average cost of those two strengths was

calculated. As the lowest available strength of many comparators is typically the most expensive per milligram, this biased the analysis against treatments with an average daily dose that exceeded the uppermost available strength. In CADTH's base case a weighted average based on the distribution of treatment strengths using IQVIA Canadian claims data[10] was used to calculate the cost per milligram of treatment, which was applied to the average daily dose. As part of a scenario analysis, the impact of treatment acquisition costs was explored using the uppermost available strength for the cost per milligram.

Recovery health costs. The manufacturer assumed no drug or health care costs would be incurred for patients achieving recovery, but this is not expected in clinical practice. The CANMAT guidelines[11] recommend maintaining treatment for an additional six to nine months after achieving symptomatic remission and an extended duration for patients at risk of recurrence. The clinical expert consulted by CADTH affirmed that high-risk patients would also likely receive an extended maintenance therapy in addition to routine follow-up visits. Based on this feedback CADTH considered recovery health costs equal to remission for drug costs, general practitioner and psychiatrist visits, and lab tests over the remainder of the time horizon in scenario analyses due to the uncertainty of this assumption.

Exclusion of relevant augmentation treatment. The manufacturer included augmentation therapy as part of second- and third-line treatment using aripiprazole and lurasidone. However, lurasidone is only approved in Canada for the treatment of depression in bipolar I disorders and is associated with higher drug costs compared to other generic augmentation strategies, a situation that favours treatment strategies with less augmentation use in second- or third-line treatment.[30] Based on the CANMAT guidelines,[11] aripiprazole, quetiapine, and risperidone were the most relevant adjunctive treatments. While the clinical expert consulted by CADTH indicated lurasidone is an emerging augmentation treatment for MDD, it would be utilized over risperidone, which is associated with additional AEs. Based on feedback from the clinical expert consulted by CADTH, an average OR (1.84) was applied in CADTH's base-case reanalyses for augmentation treatments utilized in Canada (i.e., aripiprazole, quetiapine, and lurasidone) from Zhou et al.[16] Additionally, costs associated with quetiapine were added in the economic model and equal proportions of patients were assumed to receive quetiapine (40%) or aripiprazole (40%), with lurasidone remaining unchanged.

Uncertainty of subsequent treatment. Subsequent treatments (i.e., second- and third-line treatment) were included as part of the manufacturer's base-case analysis and distributions of treatments utilized were informed using clinician input. Due to the heterogeneity of MDD patients and a lack of available data, predicting patient treatment algorithms introduced substantial uncertainty into the analyses of vortioxetine as a first-line treatment. Additionally, comparators were switched to more costly subsequent treatments in the model, favouring vortioxetine, and the actual comparative costs for vortioxetine may be overestimated. As vortioxetine is indicated for all lines of treatment in MDD,[1] and not specifically as a first-line treatment, CADTH considered a common sequencing of all patients to isolate the first-line treatment effect associated with vortioxetine as part of the base-case reanalyses. In the reanalyses, all patients received an "alternative SSRI" and "SNRI with antipsychotic augmentation" for second- and third-line treatments, respectively. The treatment distributions provided in the manufacturer's base case were applied as a scenario analysis to assess the impact of subsequent treatment sequencing on the ICUR.

CADTH Common Drug Review Reanalyses

CADTH reanalyses included the following changes to the manufacturer's base case:

1. Augmentation: inputting an average OR of included augmentation treatments (aripiprazole, quetiapine, lurasidone) for remission rate (1.84) from Zhou et al.[16] and associated drug costs
2. NMA dosing: apply unstratified ORs for remission at eight weeks and withdrawal due to AEs from Cipriani et al.[4]
3. Relapse utility: Assume same utility as baseline depression (0.54)
4. Utility decrements due to AEs: assume no utility decrement for dry mouth, sweating, dizziness, and weight gain that used a weighted average from Sullivan et al.[8]
5. a. Long-term AE probabilities: apply long-term AEs for vortioxetine from Baldwin et al.,[23] including initial eight weeks

   b. Long-term AE probabilities: apply lowest long-term AEs for weight gain and insomnia from Bet et al.[28] for comparators
6. Treatment costs: apply treatment costs per day according to dose distribution utilized in Canada
7. Same subsequent treatment for vortioxetine and comparators
8. **CADTH base case (1 + 2 + 3 + 4 + 5a + 5b + 6 + 7).**

Scenario analyses using the CADTH base case:

8a. CADTH base case + relapse utility from Young et al.[9]

8b. CADTH base case + equal remission rates at eight weeks and statistically significant withdrawal due to AEs

8c. CADTH base case + stratified doses

8d. CADTH base case + AE utility decrements from Matza et al.,[29] NICE,[7] and Young et al.[9]

8e. CADTH base case + uppermost available strength cost per milligram

8f. CADTH base case + recovery health state costs

8g. CADTH base case + manufacturer subsequent treatment distributions

8h. CADTH base case + no long-term AEs.

CADTH's sequential reanalyses are presented in Table 3, with dominated comparators removed to highlight only the efficient treatments and vortioxetine. Full results including dominated strategies are presented in Table 17. Based on the outlined changes, in CADTH's base-case vortioxetine is dominated by duloxetine and escitalopram due vortioxetine's higher costs and lower QALYs, with mirtazapine, escitalopram, and duloxetine comprising the efficiency frontier.

Table 3: Sequential Results From CADTH Reanalyses

Scenario		Treatment	Sequential ICUR ($ per QALY)
	Manufacturer base case	Bupropion	-
		Duloxetine	$50,025
		Vortioxetine	$89,785
1	Augmentation	Bupropion	-
		Duloxetine	$48,579
		Vortioxetine	$89,831
2	Unstratified dosing	Mirtazapine	-
		Bupropion	$1,386
		Duloxetine	$3,805
		Vortioxetine	$168,978
3	Relapse utility	Bupropion	-
		Duloxetine	$25,450
		Vortioxetine	$121,839
4	Utility decrements due to adverse events	Bupropion	-
		Duloxetine	$25,667
		Vortioxetine	$443,724
5a	Long-term adverse events: Baldwin et al. (2016)[23]	Bupropion	-
		Duloxetine	$50,025
		Vortioxetine	$96,940
5b	Long-term adverse events: Bet et al. (2013)[28]	Bupropion	-
		Duloxetine	$38,161
		Vortioxetine	$96,419
6	Treatment costs	Bupropion	-
		Duloxetine	$46,255
		Vortioxetine	$117,239
7	Same subsequent treatment	Bupropion	-
		Vortioxetine	$143,449
8	**CADTH base case (1 + 2 + 3 + 4 + 5a + 5b + 6 + 7)**	**Mirtazapine**	**-**
		Escitalopram	**$5,145**
		Duloxetine	**$14,542**
		Vortioxetine	**Dominated**

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

Note: Results for dominated strategies are not presented.

Exploratory scenario analyses were conducted using the CADTH base case to investigate the impact of relapse utilities, comparative efficacy and safety, stratified dosing, source of AE utility decrements, drug acquisition costs, recovery health state costs, long-term AEs, and subsequent treatment sequencing. Based on these scenarios, vortioxetine had an ICUR of $92,364 per QALY versus bupropion (equal efficacy and withdrawal due to AE) and was dominated by duloxetine, escitalopram, mirtazapine, and bupropion in all other scenarios (Table 18 in Appendix 4).

Price Reduction Analyses

Price reduction analyses were conducted using both the manufacturer and CADTH base case for all comparators. Based on the manufacturer's base case, vortioxetine would require a daily cost reduction of approximately 30% to be considered cost-effective at a willingness-to-pay threshold of $50,000 per QALY. However, when using the CADTH base case, vortioxetine was not considered cost-effective at any level of price reduction (Table 19 of Appendix 4), as the cost attributed to vortioxetine as initial treatment only represented a small proportion (< 7%) of the total one-year cost (see Table 15 for illustrative purposes).

Issues for Consideration

Vortioxetine product dosing: The manufacturer has not submitted prices for vortioxetine 15 mg tablets nor appears likely to market this strength in Canada.[31] Should Canadian patients use a 15 mg daily dosage, as seen in a proportion of clinical trial participants, and given that vortioxetine tablets do not appear to be divisible and film-coated,[1] the daily cost for these patients would be $5.76 (cost of a 10 mg and 5 mg tablet) rather than $2.95 to $3.20.

Patient adherence: The clinical expert consulted by CADTH highlighted that medication adherence and persistence is a significant concern in MDD as routine clinical practice differs from RCTs in which patients are seen regularly at set time intervals. This is supported by the published literature, which reported 18% to 37% of Canadian patients prescribed an antidepressant were non-adherent over a one-year time frame.[32,33] In addition, a matched cohort study conducted in Quebec found that only 19.7% of publicly insured patients receiving an antidepressant remained persistent with their medication.[32] This underscores the uncertainty associated with results from clinical trials versus what is observed as part of routine practice for MDD patients.

Patient Input

Input was received by four patient groups: the Canadian Mental Health Association, Mood Disorders Society of Canada, Stigma-Free Society, and Hope and Me-Mood Disorders Association of Ontario. The Canadian Mental Health Association indicated that because treatment and wellness maintenance are highly individualized, patients would be willing to continue to try new medications in hopes of finding one that works. In addition, affordable, equitable, and timely access to the full spectrum of psychological support is critical for individuals when medication alone does not resolve depression. Patients reported that medication-related side effects had a negative impact on overall quality of life and willingness and ability to seek new treatments. When a broader range of medications addressing the three facets of health (emotional, cognitive and physical) is not available to those who rely on the public system, the chances of successful treatment are seen as considerably slimmer. The manufacturer's economic submission incorporated patient concerns regarding medication-related side effects, but the facets of mental health were not specifically addressed as part of the analysis.

Respondents' depression can be accompanied by suicidal thoughts, particularly when their depressive symptoms are compounded with life- and/or work-related stress, a factor that was not assessed in the manufacturer's economic model.

Conclusions

CADTH's base case reflected changes to the following parameters: adding quetiapine as a treatment augmentation option, applying unstratified dosing ORs from Cipriani et al., altering the relapse utility, modifying long-term AE probabilities, recalculating treatment costs, and applying a common treatment sequencing. CADTH was unable to test the impact of a model structure that considered response rates. CADTH found that vortioxetine was dominated by duloxetine and escitalopram, i.e., vortioxetine was associated with greater costs and fewer QALYs. Vortioxetine was not considered cost-effective at any level of price reduction, as the cost of vortioxetine only represented a small proportion (< 7%) of the total one-year cost.

The difference in QALYs between vortioxetine and all comparators was small, suggesting similar overall treatment benefits for MDD patients. Where treatment effects are assumed to be similar for vortioxetine and treatment comparators, at a daily cost of $2.95 to $3.20, price reductions for vortioxetine of 67% to 70% would be required for the cost to equal that of generic duloxetine. To equal the cost of generic bupropion and escitalopram, the required price reductions would be 80% to 82% and 89% to 90%, respectively.

Appendix 1: Cost Comparison

The comparators in Table 4 have been deemed appropriate by clinical experts. Comparators may be recommended (appropriate) practice versus actual practice. Comparators are not restricted to drugs but may be devices or procedures. Costs are manufacturer list prices, unless otherwise specified. Existing product listing agreements are not reflected in the table and as such may not represent the actual costs to public drug plans.

Table 4: CADTH Cost Comparison of Antidepressants for Major Depressive Disorder

Drug/comparator	Strength (mg)	Dosage form	Price	Recommended daily dose (mg)	Average daily drug cost	Average annual drug cost
Vortioxetine (Trintellix)	**5 10 20**	**Tab**	**$2.8148[a] $2.9484[a] $3.2011[a]**	**10 to 20**	**$2.95 to $3.20**	**$1,077 to $1,169**
Serotonin-norepinephrine reuptake inhibitors						
Desvenlafaxine (Pristiq)	50 100	ER tablet	$2.7542[b] $2.7550[b]	50 to 100	$2.75 to $2.76	$1,006
Duloxetine (generic)	30 60	DR capsule	$0.4814 $0.9769	60	$0.98	$357
Venlafaxine (generic)	37.5 75 150	ER capsule	$0.0913 $0.1825 $0.1927	75 to 225	$0.18 to $0.38	$67 to $137
Selective serotonin reuptake inhibitors						
Citalopram (generic)[c]	20 40	tablet	$0.1332	20 to 60	$0.13 to $0.27	$49 to $146
Escitalopram (generic)	10 20	OD tablet	$1.3199 $1.4052	10 to 20	$1.32 to $1.41	$482 to $513
	10 20	tablet	$0.3109 $0.3310		$0.31 to $0.33	$114 to $121
Fluoxetine (generic)	10 20	capsule	$0.3404[d] $0.3311	20 to 60	$0.33 to $0.99	$121 to $363
Fluvoxamine (generic)[c]	50 100	tablet	$0.2105 $0.3783	100 to 300[e]	$0.38 to $1.18	$138 to $430
Paroxetine (generic)	20 30	tablet	$0.3250 $0.3453	20 to 50	$0.33 to $0.67	$119 to $245
Sertraline (generic)[c]	25 50 100	capsule	$0.1516 $0.3032 $0.3303	50 to 200	$0.30 to $0.66	$111 to $241
Noradrenaline-dopamine reuptake Inhibitor						
Bupropion (generic)	100 150	SR capsule	$0.1547 $0.2298	100 to 150	$0.15 to $0.23	$57 to $84
	150 300	ER capsule	$0.2926 $0.5853	150 to 300	$0.29 to $0.59	$107 to $214
Alpha-2 adrenergic agonist						
Mirtazapine (generic)[c]	15 30 45	OD tablet	$0.0975 $0.1950 $0.2925	15 to 45	$0.10 to $0.29	$36 to $107

Drug/comparator	Strength (mg)	Dosage form	Price	Recommended daily dose (mg)	Average daily drug cost	Average annual drug cost
	15 30 45	tablet	$0.0975[f] $0.3100 $0.2925[f]			

DR = delayed release; ER = extended release; OD = orally disintegrating; SR = sustained release.

Note: All prices are from the Ontario Drug Benefit Formulary (accessed June 2019) unless otherwise indicated, and do not include dispensing fees.[6] Annual costs are based on 365.25 days per year.

[a] Manufacturer's submitted price.[2]

[b] National wholesale price from Delta PA (June 2019).[10]

[c] Indicated for "depressive illness."

[d] Alberta Formulary (June 2019).[36]

[e] According to the fluvoxamine product monograph, doses above 150 mg should be divided so a maximum of 150 mg is given at the bedtime dose.[34]

[f] Saskatchewan Formulary (June 2019).[35]

Table 5: CADTH Comparison for Major Depressive Disorder – Atypical Antipsychotic

Drug/comparator	Strength (mg)	Dosage form	Price	Recommended daily dose (mg)	Average daily drug cost	Average annual drug cost
Aripiprazole (generic)	2 5 10 15 20 30	tablet	$0.8092 $0.9046 $1.0754 $1.2692 $1.0017 $1.0017	2 to 15	$0.81 to $1.27	$296 to $464
Lurasidone (Latuda)[a]	20 40 60 80 120	tablet	$4.3900 $4.3900 $4.3900 $4.3900 $4.3900	20 to 60	$4.39	$1,603
Quetiapine (generic)[b]	50 150 200 300 400	IR tablet	$0.2501 $0.4926 $0.6661 $0.9776 $1.3270	150 to 300	$0.49 to $0.98	$180 to $357

IR = immediate release.

Note: All prices are from the Ontario Drug Benefit Formulary (accessed June 2019) unless otherwise indicated, and do not include dispensing fees.[6] Annual costs are based on 365.25 days per year. Comparators were based on atypical antipsychotic drugs recommended as adjunctive first-line agents for nonresponse or partial response to an antidepressant as listed in the Canadian Network for Mood and Anxiety Treatment 2016 Guidelines[11] (aripiprazole, quetiapine, risperidone) or included within the manufacturer's model (aripiprazole, lurasidone).

[a] Dosing based on bipolar depression indication, Latuda is not indicated for major depressive disorder in Canada.

[b] Dosing from the Canadian Network for Mood and Anxiety Treatment 2016 Guidelines.[11]

Appendix 2: Additional Information

Table 6: Submission Quality

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?	X		
Comments Reviewer to provide comments if checking “no”	None		
Was the material included (content) sufficient?		X	
Comments Reviewer to provide comments if checking “poor”	None		
Was the submission well organized and was information easy to locate?		X	
Comments Reviewer to provide comments if checking “poor”	None		

Table 7: Authors’ Information

Authors of the pharmacoeconomic evaluation submitted to CDR

☐ Adaptation of Global model/Canadian model done by the manufacturer

☒ Adaptation of Global model/Canadian model done by a private consultant contracted by the manufacturer

☐ Adaptation of Global model/Canadian model done by an academic consultant contracted by the manufacturer

☐ Other (please specify)

	Yes	No	Uncertain
Authors signed a letter indicating agreement with entire document			X
Authors had independent control over the methods and right to publish analysis		X	

CDR = CADTH Common Drug Review.

Appendix 3: Summary of Other Health Technology Agency Reviews of Drug

Table 8: Other Health Technology Agency Findings

	NICE (November 2015)[7]	SMC (July 2016)[37]	PBAC (July 2014)[38]
Treatment	Vortioxetine 5 mg, 10 mg, and 20 mg tablets (recommended dose of 10 mg per day; 5 mg in adults 65 years and older)		
Price	£27.72 ($47.93) per 28-tablet pack	£360 ($622) per year	Redacted
Similarities with CDR submission	Efficacy informed by ITC; one-year and 24-month time horizon; decision tree and Markov model	Efficacy informed by ITC; decision tree and Markov model	Efficacy informed by ITC; cost-utility analysis
Differences with CDR submission	Second- and third-line treatment; maintenance utilities from Sapin et al. (2004);[39] UK-specific health care use and costs; alternate comparators; fourth-line subsequent treatment included	Third-line treatment; 24-month time horizon; response included in model; Scotland-specific health care costs used; alternate comparators; fourth-line subsequent treatment included	Second-line treatment; cost minimization analysis for desvenlafaxine; alternate comparators
Manufacturer's results	**Second-line** *VEN versus VOR:* £378 ($654) per QALY **Third-line** *VEN versus VOR:* £6,289 ($10,875) to £9,054 ($15,656) per QALY	*VOR versus VEN (IR and ER):* £1,997 ($3,453) and £1,351 ($2,336) per QALY *VOR versus SER:* £2,868 ($4,959) per QALY *VOR versus AGO:* dominated	Redacted
Issues noted by the review group	Concerns with ITC; little evidence for the efficacy of vortioxetine vs. comparators; unnecessarily complicated model structure; response not incorporated into the model; utility assumptions for relapse and no remission	Some relevant comparators not included; difficult to determine where QALY gain occurs; AE rates not derived by ITC but unadjusted sources; numerous weaknesses of the ITC	Noninferiority claims for vortioxetine not supported; insufficient reason to exclude SSRIs from analyses; clinical place of vortioxetine was unclear; inappropriate comparator selected; several limitations with ITC
Results of reanalyses by the review group	**Second-line** *VEN versus VOR:*[a] £4,676 to £36,434 per QALY	NA	Redacted
Recommendation	Recommended for treating major depressive episodes in adults responding inadequately to 2 antidepressants within the current episode	Accepted for restricted use in patients who have experienced an inadequate response (either due to lack of adequate efficacy and/or safety concerns) to two or more previous antidepressants	Rejected in patients who have received and not responded to an initial antidepressant medication or patients who are intolerant of or who have contraindications to another initial antidepressant therapy

AE = adverse event; AGO: agomelatine; CDR = CADTH Common Drug Review; ER = extended release; IR = immediate release; ITC = indirect treatment comparison; NA = not available; NICE = National Institute for Health and Care Excellence; PBAC = Pharmaceutical Benefits Advisory Committee; QALY = quality-adjusted life-year; SER = sertraline; SMC = Scottish Medicines Consortium; VEN = venlafaxine; VOR = vortioxetine.

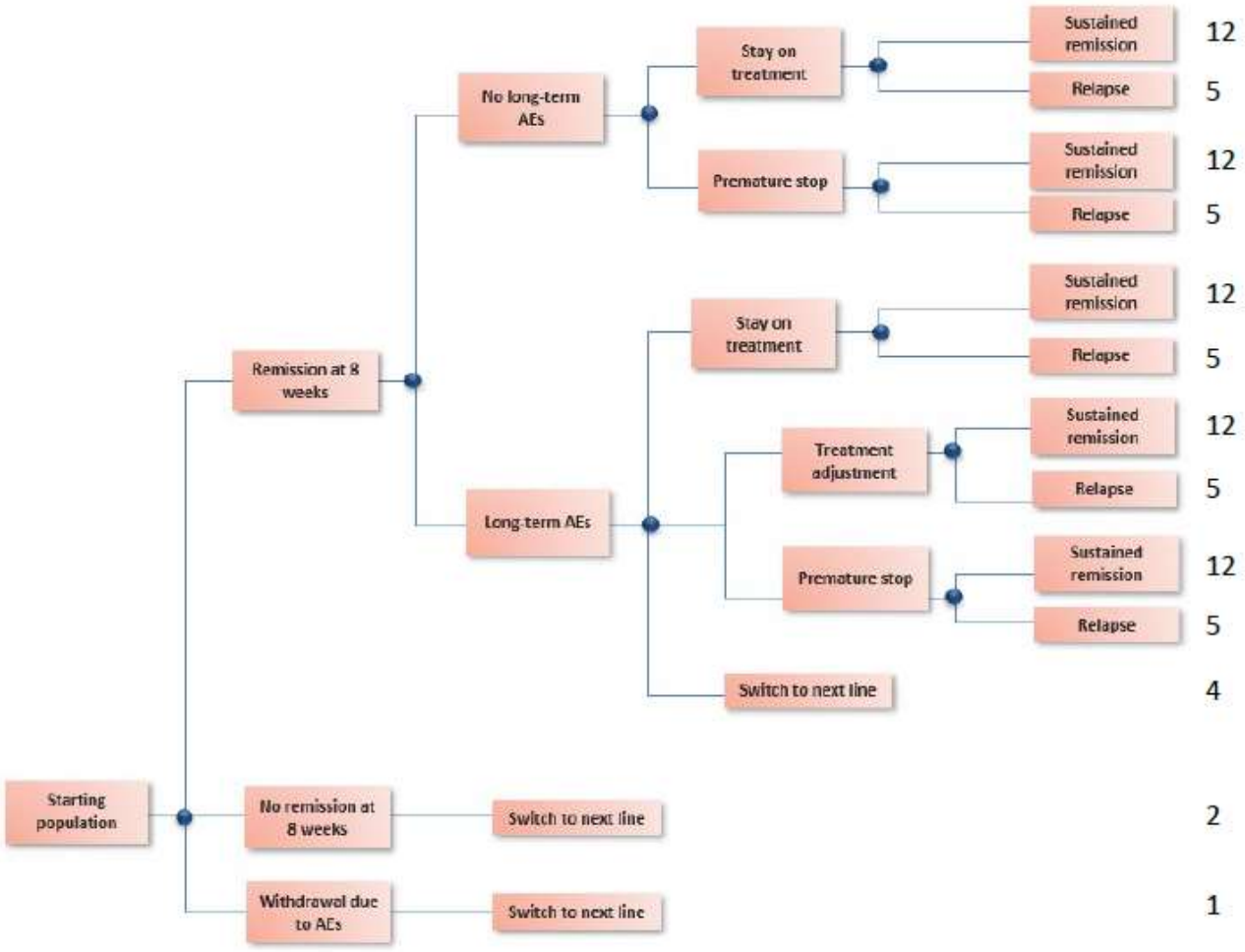
Note: Currency conversion performed using the average of 2019 monthly exchange rates from the Bank of Canada (£1 = $1.73).[40]

[a] Vortioxetine dominated in multiple scenarios.

Appendix 4: Reviewer Worksheets

Model Structure

Figure 1: Manufacturer's Decision Tree Structure

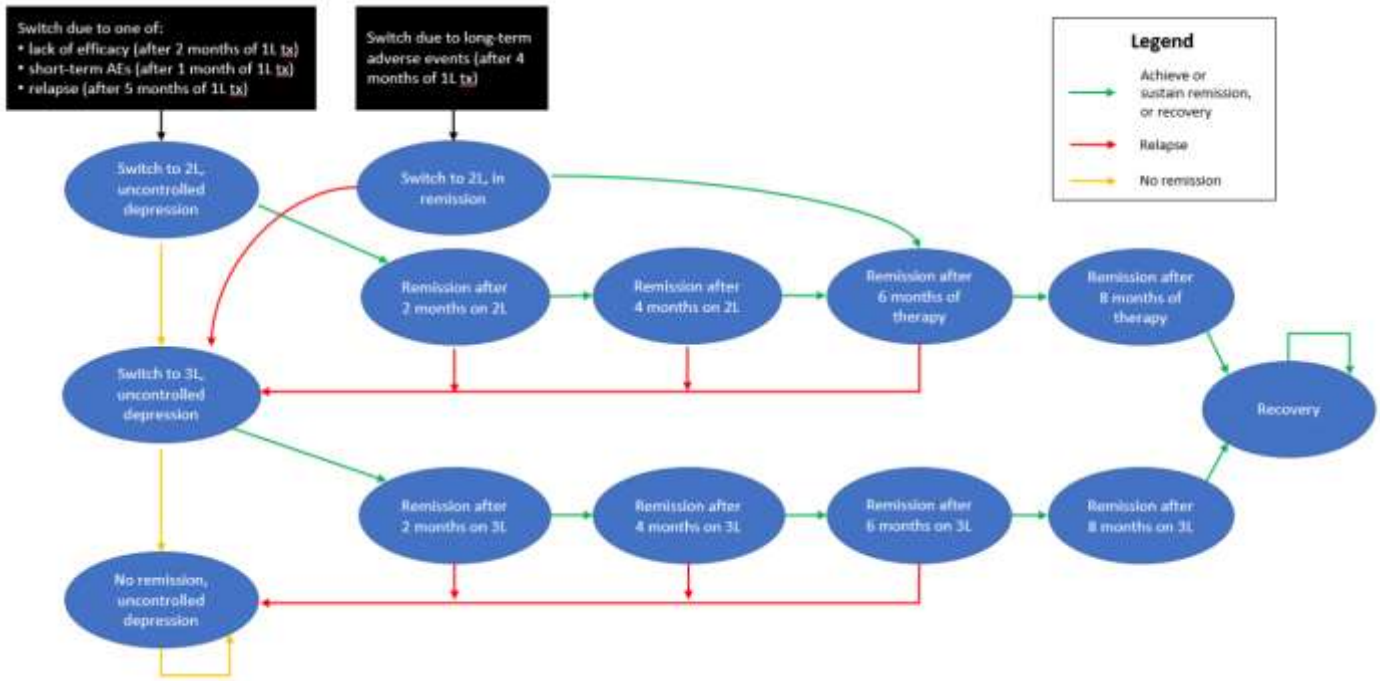


AE = adverse event.

Note: Numbers on the right represent months spent in the decision tree according to the selected pathway.

Source: Manufacturer's pharmacoeconomic submission.[2]

Figure 2: Manufacturer's Markov Model Structure



1L = first-line; 2L = second-line; 3L = third-line; AE = adverse event; Tx = treatment.

Source: Manufacturer's pharmacoeconomic submission.[2]

Treatment Effectiveness

The odds ratios from the manufacturer's network meta-analysis were applied to the placebo probabilities and transformed using the following equation:

$$Probability\ with\ antidepressant\ \frac{OR\ X\ \frac{P}{(1-P)}}{1+\left(OR\ X\ \frac{P}{(1-P)}\right)}$$

OR = odds ratio for that outcome with drug versus placebo; P = probability of outcome with placebo.

Table 9: Manufacturer Network Meta-Analyses Results – Stratified Dosing

Outcome	Drug	Median odds ratios versus placebo	Probability
Remission at 8 weeks	Placebo	[redacted]	[redacted]
	Vortioxetine	[redacted]	[redacted]
	Citalopram	[redacted]	[redacted]
	Escitalopram	[redacted]	[redacted]
	Fluoxetine	[redacted]	[redacted]
	Fluvoxamine	[redacted]	[redacted]
	Paroxetine	[redacted]	[redacted]
	Sertraline	[redacted]	[redacted]
	Duloxetine	[redacted]	[redacted]
	Venlafaxine	[redacted]	[redacted]
	Bupropion	[redacted]	[redacted]
	Mirtazapine	[redacted]	[redacted]
Withdrawal due to adverse events	Placebo	[redacted]	[redacted]
	Vortioxetine	[redacted]	[redacted]
	Citalopram	[redacted]	[redacted]
	Escitalopram	[redacted]	[redacted]
	Fluoxetine	[redacted]	[redacted]
	Fluvoxamine	[redacted]	[redacted]
	Paroxetine	[redacted]	[redacted]
	Sertraline	[redacted]	[redacted]
	Duloxetine	[redacted]	[redacted]
	Venlafaxine	[redacted]	[redacted]
	Bupropion	[redacted]	[redacted]
	Mirtazapine	[redacted]	[redacted]

Source: Manufacturer's pharmacoeconomic submission[2] and Cipriani et al. (2018).[4]

Table 10: Manufacturer's Decision Tree Probabilities After Remission on First-Line Treatment

Event	Probability
Experienced long-term adverse events	
Stay on treatment	12.5%
Treatment adjustment	12.5%
Premature treatment stop	25.0%
Switch to second-line treatment due to long-term AE	50.0%
No long-term adverse events	
Stay on treatment	80.0%
Premature treatment stop	20.0%

Source: Adapted from manufacturer's pharmacoeconomic submission.[2]

An exponential decay equation below was applied in the model for "relapse" transition probabilities:

$$N(t) = N_0 \, X \, e^{-\lambda t}$$

λ = exponential decay constant; t = number of months elapsed; N_0 = starting number of patients; N(t) = number of patients who have not elapsed after t months.

Health-State Utilities

Table 11: Health-State Utilities

Health state	Utility value (EQ-5D)	Data sources and notes
Baseline depression	0.54	REVIVE trial
Remission	0.85	REVIVE trial
No remission	0.62	REVIVE trial – weighted average of patients failing to achieve remission at eight weeks
Relapse	0.62	Assumed same as no remission
Recovery	0.85	Assumed same as recovery

EQ-5D = EuroQol 5-Dimensions.

Source: Manufacturer's pharmacoeconomic submission.[2]

Adverse Events

The probability of experiencing at least one long-term AE was derived using the equation below:

Long-term AE% = 1 − (1 − Long-term sexual dysfunction%) × (1 − Long-term insomnia%) × (1 − weight gain%)

Table 12: Short- and Long-Term Adverse Event Probabilities

AE	VOR	CIT	ESC	FLU	FLU	PAR	SER	DUL	VEN	BUP	MIR
Short-term											
Sexual dysfunction %	1.75	6.24	6.36	8.87	6.12	9.08	12.77	3.77	8.38	0.00	2.85
Dry mouth %	5.95	19.40	6.60	9.50	26.00	17.52	16.30	15.00	19.42	16.36	24.72
Nausea %	25.88	20.60	15.20	20.36	37.00	24.95	26.10	20.00	35.47	12.93	7.39
Sweating %	1.65	10.50	3.40	7.80	11.00	10.10	8.40	6.00	12.52	3.35	4.06
Headache %	13.12	10.83	15.71	28.06	22.00	19.43	20.30	15.59	25.25	27.15	13.06
Somnolence %	3.00	17.30	4.10	12.36	26.00	23.05	13.40	7.00	21.51	2.29	53.64
Diarrhea %	6.21	8.10	8.40	14.03	6.00	12.95	17.70	8.00	8.06	5.04	6.14
Insomnia %	2.48	8.24	8.20	16.29	14.00	14.10	16.40	11.00	17.77	9.81	6.55
Dizziness %	5.95	6.77	6.30	11.04	15.00	13.52	11.70	9.00	19.21	7.87	7.28
Long-term											
Sexual dysfunction %	2.27	23.00	23.00	23.00	23.00	23.00	23.00	31.00	31.00	0.00	10.00
Insomnia %	3.30	7.00	7.00	7.00	7.00	7.00	7.00	10.00	10.00	16.00	5.00
Weight gain %	4.40	19.00	19.00	19.00	19.00	19.00	19.00	17.00	17.00	0.00	29.00

AE = adverse event; BUP = bupropion; CIT = citalopram; DUL = duloxetine; ESC = escitalopram; FLU = fluoxetine; FLU = fluvoxamine; MIR = mirtazapine; PAR = paroxetine; SER = sertraline; VEN = venlafaxine.

Source: Adapted from manufacturer's pharmacoeconomic submission.[2]

Summary of Manufacturer Data Sources

Table 13: Model Data Sources

Data input	Description of data source	Comment
Efficacy and natural history	The manufacturer submitted an NMA based on the findings from Cipriani et al. (2018);[4] however results were stratified according to dose. The NMA reported median ORs for both remission and withdrawal due to of first-line treatments compared to placebo in the decision tree. Clinical expert estimates were used to inform probabilities after remission on first-line treatment.	Uncertain. Although the manufacturer's NMA does leverage both placebo-controlled and head-to-head studies, the analysis further stratifies the evidence base and more heavily relies on biased and dispersed head-to-head comparisons, which was noted by Cipriani et al. (2018). The reduction in evidence for each group introduces greater uncertainty to estimates [redacted]. It was therefore considered more appropriate to use the NMA results presented by Cipriani et al. (2018) as part of the CADTH base-case reanalyses for vortioxetine and include the manufacturer NMA stratified according to dose in scenario analyses.
	Transition probabilities for patients relapsing and continuing first-line treatment were obtained from Limosin et al. (2004).[15] Patients prematurely stopping treatment following a relapse on first-line treatment followed probabilities derived from the STAR*D trial.[14] The STAR*D trial[14] was also used to inform the remission and relapse probabilities for all second- and third-line treatments.	Uncertain. The use of the STAR*D trial[14] in the Canadian setting is limited as 100% of patients received citalopram as first-line treatment. According to the CANMAT guidelines,[11] citalopram is one of six SSRIs recommended for first-line treatment and applicability of the results to SNRI treatments, bupropion, and mirtazapine is uncertain. Additionally, subsequent treatments were not aligned with Canadian clinical practices as STAR*D excluded SNRIs and relevant augmentation treatments.
	A median OR of 1.84 (95% CrI, 1.37 to 2.53) obtained from Zhou et al. (2015)[16] was applied to remission rates of second- and third-line treatments receiving augmentation with an atypical antipsychotic.	Source acceptable. Based on feedback from the clinical expert consulted by CADTH, an average OR (1.84) of augmentation treatments utilized in Canada (aripiprazole, quetiapine, and lurasidone) from Zhou et al. (2015)[16] was applied in CADTH's reanalyses.
Utilities	Derived from REVIVE trial and applied a UK preference weight to the EQ-5D data.[23]	Acceptable.
	Utility decrements due to AEs were obtained from Sullivan et al. (2004)[8] and applied for one month.	Source acceptable. However, median utility decrements were applied instead of mean estimates.[41]
AEs	Short-term AE probabilities were obtained from relevant product monographs, published literature, or Cochrane reviews. Baldwin et al. (2016),[23] a meta-analysis of 10 randomized placebo-controlled trials, was used to inform probabilities of sexual AEs and headaches with vortioxetine. It was assumed bupropion had a 0% probability of causing sexual AEs and was verified by clinical experts.	Uncertain. Unadjusted AE probabilities were derived from multiple sources, with only a meta-analysis conducted for trials studying vortioxetine.[28] Based on these sources there is substantial uncertainty of the comparative rates of AEs between treatments.
	Long-term AEs for all comparators were informed by Bet et al. (2013),[28] a naturalistic study conducted in the Netherlands, and vortioxetine	Uncertain. A key difference between these studies is the use of patient-perceived AEs used in Bet et al. (2013) compared with the open-label trials analysis

Data input	Description of data source	Comment
	used probabilities reported by Baldwin et al. (2016).[23] It was assumed venlafaxine and duloxetine would have the same long-term AE probabilities.	by Baldwin et al. (2016), which were documented by the study investigators using the standardized Medical Dictionary for Regulatory Activities. The extent of concurrence between self-reported AE measures with standardized reporting methodologies and whether these represent the expected frequency of long-term AEs is therefore uncertain.
Resource use and costs		
Drug	Average daily doses were calculated based on trial characteristics in the Cipriani et al. (2018)[4] data set and weighted by sample size. Dosing was stratified according to trials utilizing doses at or above the WHO DDD.[42]	Acceptable.
	A weighted average was applied to doses between available strengths. A cost per milligram in excess (lowest available strength) was applied to doses exceeding the highest available strength.	Inappropriate. This methodology is biased against fixed price per mg treatments as the weighted average dosing price of non-fixed price per milligram treatments is typically below the lowest available strength.
	Vortioxetine cost was based on the manufacturer's submitted price.	Uncertain. A 5 mg strength pricing was not included in the manufacturer's model despite being available in Canada. Additionally, patients 65 years of age and older are recommended to receive 5 mg as a starting dose, which was not reflected in the evaluation.[1]
	Comparator drug acquisition costs were obtained from the ODB Formulary.[6]	Acceptable.
	Aripiprazole and lurasidone were considered as adjunctive options for second- and third-line treatments based on expert opinion.	Inappropriate. Based on CANMAT[11] guidelines and clinical expert feedback, quetiapine is used as adjunctive treatment in Canada and should be included in the economic model.
Administration	No treatment administration costs were assumed for vortioxetine and all comparators.	Acceptable, based on feedback from clinical expert.
AEs	Frequencies of GP visits and daily drug usage were obtained from clinical expert opinion. Costs for GP visits were obtained from the Ontario SoB and drug costs from the ODB formulary.	Sources acceptable.
Health state	Frequencies of GP visits, psychiatrist visits, laboratory tests, inpatient hospitalizations, and ER visits were obtained from clinical expert opinions according to health state. Costs were obtained from the OCCI[25] for hospitalizations and ER visits and Ontario SoB[26,27] for others.	Sources acceptable.

AE = adverse event; CANMAT = Canadian Network for Mood and Anxiety Treatment; CrI = credible interval; DDD = defined daily dose; EQ-5D = EuroQol 5-Dimensions questionnaire; ER = emergency room; GP = general practitioner; NICE = National Institute for Health and Care Excellence; NMA = network meta-analysis; OCCI = Ontario Case Costing Initiative; ODB = Ontario Drug Benefit; OR = odds ratio; SoB = schedule of benefits; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; STAR*D = Sequenced Treatment Alternative to Relieve Depression.

Summary of Key Assumptions

Table 14: Manufacturer's Key Assumptions

Assumption	Comment
Baseline characteristics had no influence on model outcomes.	Acceptable, based on feedback from clinical expert.
100% treatment compliance was assumed.	Uncertain. Although 100% treatment compliance was assumed to simplify the model inputs, the clinical expert consulted by CADTH indicated it would be unreasonable to expect all patients to be compliant in practice. This is also supported by the published literature,[32,33,43] which reported 18% to 37% of Canadian patients prescribed an antidepressant were non-adherent over a one-year time frame.
Switch to second-line treatment due to short-term AEs occurred after one month, switch due to lack of efficacy after two months, and switch due to long-term AEs after four months from initiating treatment. First-line relapse occurred after five months of starting treatment.	Acceptable, based on feedback from clinical expert.
Patients in the "recovery" health state were considered "cured" of MDD and would not incur drug or health care costs. Additionally, patients would not experience any relapses in this health state.	Uncertain. The clinical expert and CANMAT guidelines highlighted that patients with a previous history of recurring episodes or persistent depression would be advised to continue maintenance treatment with an antidepressant beyond six months. Additionally, patients would likely continue to receive periodic visits with their physician as part of follow-up. Inappropriate. Based on clinical expert feedback, patients achieving stable remission after six months are more likely to maintain a durable response, although some patients will still relapse after achieving recovery.
All antidepressants had equal efficacy and probability of relapse in second- and third-line treatment.	Acceptable. Given the uncertainty associated with the applicability of the STAR*D trial to the Canadian setting and feedback from the clinical expert, CADTH considered this assumption reasonable.
Individual AE probabilities did not affect probabilities of switching to second-line treatment due to short-term AEs. Additionally, 100% of patients withdrawing from first-line due to short-term AEs (as informed by the NMA) were assumed to switch to second-line.	Uncertain. The clinical expert indicated the majority of patients would be offered second-line treatment due to intolerability of first-line treatment; however, a subgroup of patients would likely be reluctant to try additional antidepressants.
Relapses occurred at the midpoint between "remission" and "recovery" health states (i.e., three months).	Reasonable, based on clinical expert feedback.
"Relapse" and "recovery" health states had the same utility value as "no remission" and "remission," respectively.	Inappropriate. In a previous submission of vortioxetine to NICE,[7] the ERG considered relapsing patients to experience a recurrence of moderate-to-severe major depression and applied a baseline depression utility for relapse patients (0.54). The clinical expert also confirmed patients would likely experience a complete regression to baseline during a relapse; however, this may not be representative for all patients.
AE utility decrements not reported by Sullivan et al. (2004)[8] were calculated using a weighted average of all AEs (0.085). Somnolence was assumed to be equivalent to drowsiness (0.085).	Inappropriate. The weighted utility decrements applied in the model were biased in favour of vortioxetine as these were applied to AEs with substantial discrepancies in the frequency of occurrence versus most comparators (i.e., dry mouth, sweating, somnolence, and weight gain). Additionally, the magnitude of the weighted decrement (0.085) was greater than most AEs (i.e., sexual dysfunction/AEs, nausea, and

Assumption	Comment
	diarrhea) applied in the model, further highlighting the uncertainty of these estimates.
All patients experiencing an AE would visit a GP.	Acceptable, based on feedback from clinical expert.
Both short- and long-term AEs were assumed to only occur in first-line treatment.	Inappropriate. The clinical expert indicated it would be highly unlikely AEs would only occur within first-line treatments and patients would likely experience a new set of AEs when switching treatments.
A one-year time horizon is sufficient to account for differences in the costs and effects of different first-line treatments.	Reasonable. However, a one-year time horizon may not be sufficient to reflect the heterogeneity associated with MDD and the variability in long-term remission maintenance by patients. Additionally, the CANMAT guidelines highlight that patients with risk factors for recurrence would likely benefit from the extension of maintenance treatment to two years or beyond.[11]
Patient mortality was not expected to occur in a one-year time horizon.	Uncertain. The clinical expert highlighted MDD patients would be at risk of suicide during the one-year time horizon, with inpatients being more likely to attempt suicide compared to outpatients. Previous cost-effectiveness models have also incorporated suicide as patients with mental disorders were considered a high-risk population.[44-46]

AE = adverse event; CANMAT = Canadian Network for Mood and Anxiety Treatments; ERG = Evidence Review Group; GP = general practitioner; MDD = major depressive disorder; NICE = National Institute for Health and Care Excellence; NMA = network meta-analysis; STAR*D = Sequenced Treatment Alternative to Relieve Depression.

Manufacturer's Results

Table 15: Cost Breakdown of Manufacturer's Base Case

	Drug costs	Consultation costs	Hospitalization costs	Total switch costs	AE costs	Total cost
Bupropion	$58	$693	$230	$2,966	$53	$4,000
Citalopram	$12	$706	$249	$3,128	$77	$4,171
Duloxetine	$98	$703	$239	$2,939	$79	$4,058
Escitalopram	$30	$710	$244	$3,011	$64	$4,060
Fluoxetine	$50	$708	$248	$3,095	$98	$4,199
Fluvoxamine	$54	$687	$236	$3,061	$108	$4,145
Mirtazapine	$23	$701	$239	$2,994	$70	$4,028
Paroxetine	$32	$704	$241	$3,004	$105	$4,087
Sertraline	$31	$705	$246	$3,091	$111	$4,185
Venlafaxine	$22	$694	$237	$2,986	$121	$4,061
Vortioxetine	**$299**	**$695**	**$232**	**$3,097**	**$48**	**$4,372**

AE = adverse event.

Source: Adapted from manufacturer's pharmacoeconomic submission.[2]

Table 16: Summary of Results of the Manufacturer's Base Case

	Total costs	Total QALYs	ICUR (vortioxetine versus comparator)	Sequential ICUR ($ per QALY)
Non-dominated strategies				
Bupropion	$4,000	0.6886	$79,882	-
Duloxetine	$4,058	0.6898	$89,785	$50,025
Vortioxetine	$4,372	0.6933	-	$89,785
Dominated strategies				
Citalopram	$4,171	0.6796	$14,643	Dominated by bupropion; mirtazapine; duloxetine; escitalopram
Escitalopram	$4,060	0.6881	$60,335	Dominated by bupropion; duloxetine
Fluoxetine	$4,199	0.6771	$10,700	Dominated by bupropion; mirtazapine; duloxetine; escitalopram; venlafaxine; paroxetine; citalopram
Fluvoxamine	$4,145	0.6758	$12,977	Dominated by bupropion; mirtazapine; duloxetine; escitalopram; venlafaxine; paroxetine
Mirtazapine	$4,028	0.6821	$30,596	Dominated by bupropion
Paroxetine	$4,087	0.6794	$20,512	Dominated by bupropion; mirtazapine; duloxetine; escitalopram
Sertraline	$4,185	0.6765	$11,122	Dominated by bupropion; mirtazapine; duloxetine; escitalopram; venlafaxine; paroxetine; citalopram
Venlafaxine	$4,061	0.6788	$21,487	Dominated by bupropion; mirtazapine; duloxetine; escitalopram

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

Source: Adapted from manufacturer's pharmacoeconomic submission.[2]

CADTH Common Drug Review Reanalyses

Base-Case Results

Table 17: CADTH Base-Case Sequential Results

Scenario	Treatment	Total costs	Total QALYs	Pairwise ICUR (vortioxetine versus comparator)	Sequential ICUR ($ per QALY)
CADTH base case (1 + 2 + 3 + 4 + 5a + 5b + 6 + 7)	**Non-dominated strategies**				
	Mirtazapine	$4,066	0.653	$119,187	-
	Escitalopram	$4,085	0.657	Dominates vortioxetine	$5,145
	Duloxetine	$4,105	0.658	Dominates vortioxetine	$14,542
	Dominated strategies				
	Bupropion	$4,089	0.655	$959,121	Dominated
	Citalopram	$4,195	0.650	$29,852	Dominated
	Fluoxetine	$4,231	0.646	$14,689	Dominated
	Fluvoxamine	$4,123	0.651	$48,975	Dominated
	Paroxetine	$4,118	0.652	$59,513	Dominated
	Sertraline	$4,214	0.648	$18,847	Dominated
	Venlafaxine	$4,115	0.650	$41,411	Dominated
	Vortioxetine	$4,367	0.656	-	Dominated

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

Scenario Results

Table 18: Results from CADTH Scenario Analyses

	Scenario	Treatment	Pairwise ICUR (vortioxetine versus comparator)	Sequential ICUR ($ per QALY)
8a	Relapse utility from Young et al. (2017)[9]	Mirtazapine	$110,824	-
		Escitalopram	Dominates vortioxetine	$5,140
		Duloxetine	Dominates vortioxetine	$16,385
		Vortioxetine	-	Dominated
8b	Equal remission at eight weeks and statistically significant withdrawal due to AEs	Bupropion	$92,364	-
		Vortioxetine	-	$92,364
8c	Stratified dosing	Bupropion	Dominates vortioxetine	-
		Duloxetine	Dominates vortioxetine	$168,476
		Vortioxetine	-	Dominated
8d	AE utility decrements from Matza et al. (2019)[29]	Mirtazapine	$98,473	-
		Escitalopram	Dominates vortioxetine	$4,727
		Duloxetine	Dominates vortioxetine	$17,028
		Vortioxetine	-	Dominated
8e	Uppermost available strength cost per mg	Mirtazapine	$76,533	-
		Escitalopram	Dominates vortioxetine	$3,417
		Duloxetine	Dominates vortioxetine	$24,667
		Vortioxetine	-	Dominated
8f	Recovery health-state costs	Mirtazapine	$117,615	-
		Escitalopram	Dominates vortioxetine	$5,724
		Duloxetine	Dominates vortioxetine	$16,329
		Vortioxetine	-	Dominated
8g	Manufacturer subsequent treatment	Mirtazapine	$63,436	-
		Duloxetine	Dominates vortioxetine	$2,587
		Vortioxetine	-	Dominated
8h	No long-term AEs	Mirtazapine	$168,800	-
		Escitalopram	Dominates vortioxetine	$410
		Duloxetine	Dominates vortioxetine	$4,807
		Vortioxetine	-	Dominated

AE = adverse event; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

Note: Results for dominated strategies are not presented.

Price Reduction Reanalyses

Table 19: CADTH Price Reduction Scenarios – Sequential Results

Scenario	Manufacturer base-case ICUR ($ per QALY)	CADTH base-case ICUR ($ per QALY)
Vortioxetine submitted price	λ < $50,025: bupropion $50,025 < λ < $89,785: duloxetine λ ≥ $89,785: vortioxetine	λ < $5,145: mirtazapine $5,145 < λ < $14,542: escitalopram λ ≥ $14,542: duloxetine
80% reduction	λ < $6,804: bupropion λ ≥ $6,804: vortioxetine	λ < $5,145: mirtazapine $5,145 < λ < $14,542: escitalopram λ ≥ $14,542: duloxetine
85% reduction	λ < $2,237: bupropion λ ≥ $2,237: vortioxetine	λ < $5,145: mirtazapine $5,145 < λ < $14,542: escitalopram λ ≥ $14,542: duloxetine
90% reduction	All comparators dominated by vortioxetine	λ < $5,145: mirtazapine $5,145 < λ < $14,542: escitalopram λ ≥ $14,542: duloxetine
95% reduction	All comparators dominated by vortioxetine	λ < $5,145: mirtazapine $5,145 < λ < $14,542: escitalopram λ ≥ $14,542: duloxetine

λ = willingness-to-pay threshold; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life year.

Note: Results for dominated strategies are not presented.

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