Common Drug Review
Pharmacoeconomic Review Report

November 2016

Drug	aripiprazole (Abilify)
Indication	As an adjunct to antidepressants for the treatment of major depressive disorder (MDD) in adult patients who had an inadequate response to prior antidepressant treatments during the current episode
Listing request	As per indication
Manufacturer	Bristol-Myers Squibb Canada[a]

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ABBREVIATIONS

AAP	atypical antipsychotic
ADT	antidepressant therapy
AE	adverse event
BSC	best supportive care
CDR	CADTH Common Drug Review
CUA	cost-utility analysis
HAM-D	Hamilton Depression Rating Scale
ICUR	incremental cost-utility ratio
ITC	indirect treatment comparison
MADRS	Montgomery–Åsberg Depression Rating Scale
MDD	major depressive disorder
MDE	major depressive episode
MDSC	Mood Disorders Society of Canada
ODBF	Ontario Drug Benefit Formulary
RCT	randomized controlled trial

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	aripiprazole (Abilify)
Study Question	Primary analysis was to compare the use of aripiprazole with the use of quetiapine in the adjunctive treatment of MDD in adult patients who had an inadequate response to prior antidepressant treatments during the current episode. A secondary analysis to compare aripiprazole with other atypical antipsychotics in MDD was also undertaken.
Type of Economic Evaluation	Cost-utility analysis
Target Population	Adult patients with MDD
Treatment	Aripiprazole dosed as per the product monograph
Outcome(s)	Life-years, QALYs, number of major depressive episodes
Comparators	Primary: quetiapine Secondary: quetiapine, olanzapine, risperidone
Perspective	Public payer in Canada
Time Horizon	Lifetime (number of years not specified)
Manufacturer's Results (Base Case)	In the primary analysis, the incremental costs and QALYs for aripiprazole versus quetiapine are $97 and 0.020, respectively, with an incremental cost per QALY gained (by ICUR) of $4,829. In the secondary analysis, risperidone dominated all other treatments (aripiprazole, quetiapine, olanzapine).
Key Limitations and CDR Estimate(s)	• Uncertain comparative efficacy between aripiprazole and quetiapine. The comparative effectiveness was obtained from ITC; CDR identified several limitations and potential sources of bias. Based on ITC results, ICUR for aripiprazole compared with quetiapine ranged from dominant to dominated by quetiapine. • Assumptions regarding quetiapine use may not be appropriate. The model assumed that quetiapine would be used at 300 mg/d; however, quetiapine can be used in a range of 150 mg/d to 300 mg/d for the treatment of a MDE. Also, the model assumed that quetiapine would be used as adjunctive treatment with ADT, while it can be used either as monotherapy or add-on. • Improbable lifetime horizon length. The submitted model used lifetime horizon of 999 years. Assuming a lifetime horizon length of 40 years, CDR estimate of ICUR is $4,678. • CDR reanalysis assumed a range of quetiapine doses, 50% of patients would use quetiapine as monotherapy, and 40-year time horizon. The reanalysis showed that aripiprazole was associated with an additional 0.020 QALYs per patient and an addition cost of $165 compared with quetiapine, leading to an incremental cost per QALY gained of $8,231.

ADT = antidepressant therapy; CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; ITC = indirect treatment comparison; MDD = major depressive disorder; MDE = major depressive episode; QALY = quality-adjusted life-year.

EXECUTIVE SUMMARY OF THE PHARMACOECONOMIC SUBMISSION

Background

The review of aripiprazole (Abilify) is for the adjunctive treatment of major depressive disorder (MDD) in adult patients who had an inadequate response to prior antidepressant therapy during the current episode. Aripiprazole is an oral drug administered as adjunctive treatment for patients already taking an antidepressant, at an initial dose of 2 mg to 5 mg per day, which can be titrated up to 15 mg per day with maximum dose adjustments of up to 5 mg per day occurring gradually, at intervals of no less than one week. The submitted price varies depending on dose: 2 mg = $3.0013; 5 mg = $3.3783; and 10 mg, 15 mg, 20 mg, and 30 mg = $3.8933.[1] The submitted prices are in some cases substantially less than the list prices of several public drug formularies.

Aripiprazole was reviewed twice previously by CADTH Common Drug Review (CDR): in 2010 for schizophrenia and in 2011 for schizophrenia and related psychotic disorders.[2,3] In 2011, the Canadian Expert Drug Advisory Committee recommended that aripiprazole be listed with clinical conditions, superseding the 2010 recommendation not to list aripiprazole.

Summary of Economic Analysis

The manufacturer submitted a cost-utility analysis based on a patient-level simulation model.[4] The primary analysis compares aripiprazole with quetiapine (Seroquel extended release [XR]), while a secondary analysis compares aripiprazole with quetiapine, risperidone, and olanzapine.[4] The manufacturer considers a patient lifetime time horizon, with four possible health states: major depressive episode (MDE) in the acute phase, remission, symptom-free, and death. Patients enter the model in the MDE state (representative of the randomized controlled trials of aripiprazole) and remain in the MDE state for at least six weeks, until remission or death. Clinical information to inform the model was based on an indirect treatment comparison (ITC) of aripiprazole with other specified atypical antipsychotic drugs (AAPs; quetiapine, risperidone, and olanzapine) used in the treatment of MDD. Transition to remission was determined by random probability, with success based on treatment-specific remission rates drawn from the ITC using a Monte Carlo method. Patients are allowed to receive up to two courses of treatment with the same AAP. If the patient does not respond following the second course, the patient goes on to best supportive care. (Although other therapeutic measures are available in Canada, the manufacturer assumed no cost and effect given the lack of information available.) After nine months of remission, patients transition to the symptom-free health state. Mortality can occur at any time, and from any health state in the model. The analysis is conducted from the perspective of the health care payer. Costs were applied per week, according to the health state. Utility values were sourced from published literature.

Results of Manufacturer's Analysis

- Aripiprazole is associated with an additional 0.020 QALYs per patient and an addition cost of $97 compared with quetiapine, leading to an incremental cost per QALY gained of $4,829.
- Risperidone dominates, being both cheaper and more effective than aripiprazole, quetiapine, and olanzapine.

Interpretations and Key Limitations

CDR identified several limitations of the model:

- **Uncertain comparative efficacy:** The manufacturer submitted an ITC to evaluate the relative efficacy of quetiapine and aripiprazole in terms of remission. The ITC contained several limitations that

hindered the interpretability of results. The impact of uncertainty around the comparative effectiveness, in terms of remission, was partially evaluated in the manufacturer's sensitivity analysis; it was reported that aripiprazole would be dominated by quetiapine when the upper efficacy limit of quetiapine versus aripiprazole was considered.

- **Assumptions regarding quetiapine use may not be appropriate:** The manufacturer assumed that quetiapine would be used at 300 mg per day; however, quetiapine can be used from 150 mg to 300 mg per day for the treatment of a MDE.[5,6] Furthermore, the model assumed that quetiapine would be used as adjunctive therapy only; however, quetiapine could be used as monotherapy or add-on, with higher-level evidence supporting its use as monotherapy.[5,6] Therefore, the model seemed to overestimate the costs associated with quetiapine, which would underestimate the incremental cost-utility ratio (ICUR) of aripiprazole compared with quetiapine.
- **Model time horizon:** The submitted model uses a time horizon of 999 years. This value is extremely high, and results in an underestimation of the ICUR of aripiprazole compared with quetiapine. The model assumed a starting age of 45 years for the simulated patients; 40 years lifetime horizon would therefore be appropriate assuming a life expectancy of 85 years.

Results of CADTH Common Drug Review Analysis

Given the issues identified with manufacturer's model, CDR conducted a reanalysis based on:

- A lifetime horizon of 30 to 55 years, based on life expectancy of 75 to 100 years
- An equal distribution of the three quetiapine doses 150 mg, 200 mg, and 300 mg per day among the simulated patients, instead of 300 mg per day only
- Treatment of half of the patients with quetiapine as monotherapy instead of adjunct to other antidepressant medications.

Based on the reanalysis, aripiprazole was associated with an additional 0.020 QALYs per patient and an addition cost of $165 compared with quetiapine, leading to an incremental cost per QALY gained of $8,231.

Issues for Consideration

Based on available evidence, aripiprazole did not differ statistically from quetiapine in terms of rates of remission, and the numerical difference between the two comparators generated a minimal difference in terms of QALYs (0.020). This difference might not be sufficient to justify the price difference between aripiprazole and quetiapine ($3.00 to $3.89 daily for aripiprazole versus $0.40 to $1.54 daily for quetiapine).

In Canada, two AAPs have been approved for treatment of MDD, quetiapine and aripiprazole. Olanzapine and risperidone are two other AAPs that are available in Canada but do not have a Health Canada indication for the treatment of MDD. The manufacturer's analysis showed that risperidone dominated quetiapine, aripiprazole, and olanzapine.

Conclusions

Based on the results of the manufacturer's indirect treatment comparison, the efficacy of aripiprazole and quetiapine appear similar, which would render aripiprazole more costly than quetiapine. There is, however, considerable uncertainty around the magnitude and direction of the numerical differences. CDR identified several limitations in the manufacturer's analysis; which when adjusted for in the model resulted in a higher incremental cost per QALY gained of $8,231 for aripiprazole versus quetiapine.

REVIEW OF THE PHARMACOECONOMIC SUBMISSION

1. INTRODUCTION

1.1 Study Question

A cost-utility analysis (CUA) was conducted to compare the use of aripiprazole to the use of quetiapine in the adjunctive treatment of major depressive disorder (MDD) in adult patients who had an inadequate response to prior antidepressant therapy (ADT) during the current episode. A secondary analysis was conducted comparing adjunctive treatment with aripiprazole to adjunctive treatment with quetiapine, olanzapine, or risperidone.

1.2 Treatment

Aripiprazole (Abilify), as an adjunct to ADT.

1.3 Comparators

The primary comparator for the economic evaluation was quetiapine extended release (Seroquel XR), as this is the only atypical antipsychotic (AAP) approved by Health Canada for specific use in MDD, alone or as an adjunct to ADT. Quetiapine is currently funded as a general benefit across all provinces in Canada.

The approved dose for quetiapine ranges from 50 mg per day up to 300 mg per day, while the submitted model assumed that quetiapine would always be used at its highest approved dose (300 mg per day).[6] The manufacturer justified the use of the highest dose by arguing that the efficacy profile of aripiprazole was more aligned with quetiapine 300 mg per day; however, this was based on an indirect treatment comparison (ITC) submitted by the manufacturer, in which the results of quetiapine 150 mg per day and 300 mg per day were pooled as one intervention. Therefore, assuming that all patients would be treated with quetiapine 300 mg per day would create a bias against quetiapine due to the higher price of quetiapine 300 mg per day and its lower efficacy. Furthermore, the model assumed that quetiapine would always be used as an adjunct to ADT; however, some patients could benefit from quetiapine when used as monotherapy.[7]

Several other AAPs (asenapine, clozapine, lurasidone, olanzapine, paliperidone, and risperidone) are also available in Canada for the treatment of mental health disorders. According to the manufacturer's report, IMS Brogan data indicates that olanzapine and risperidone, in particular, are often used off-label in the adjunctive treatment of non-responsive MDD; olanzapine has approximately 14% of the market share in Ontario for the treatment of MDD, while risperidone has approximately 13% of the market share in Ontario.[4] Olanzapine and risperidone, along with quetiapine, were included in a scenario analysis against aripiprazole.

1.4 Type of Economic Evaluation

The manufacturer undertook a CUA. This is appropriate given the potential impact this disorder may have on quality of life, according to Canadian Agency for Drugs and Technologies in Health (CADTH) *Guidelines for the Economic Evaluation of Health Technologies*.[8]

The analysis takes a public payer perspective. This is appropriate according to CADTH guidelines.[8] A scenario analysis was conducted from the societal perspective.

1.5 Population

The Health Canada indication for aripiprazole is as an adjunct to antidepressants for the treatment of MDD in adult patients who had an inadequate response to prior antidepressant treatments during the current episode. The manufacturer requested reimbursement for the Health Canada indication.

2. METHODS

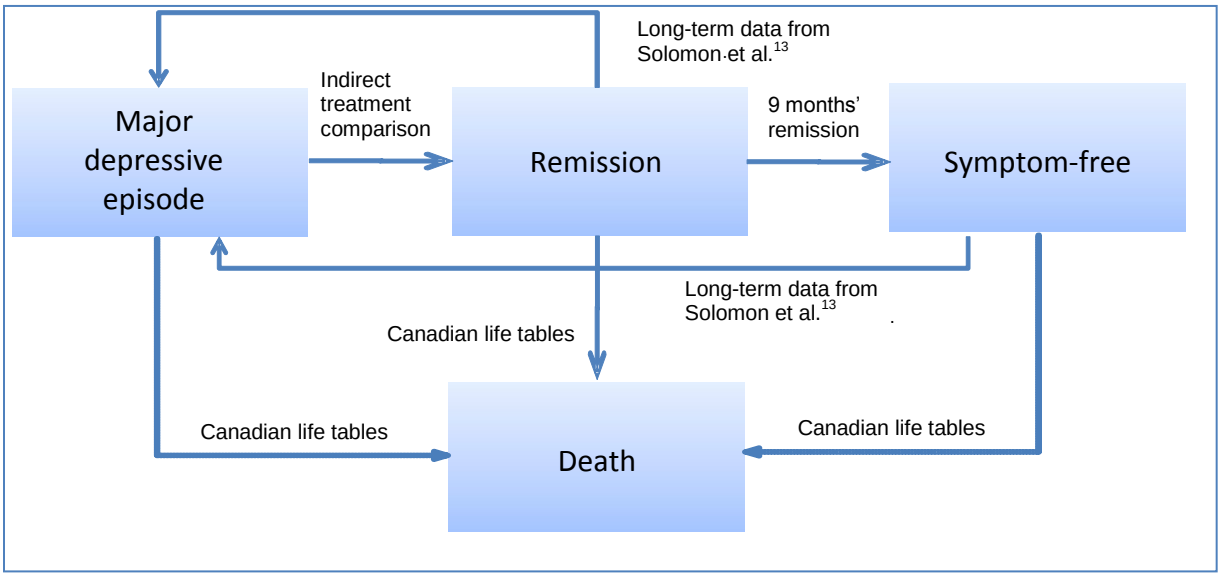
2.1 Model Structure

The model uses a patient-level simulation (e.g., Monte Carlo, stochastic) model to conduct the economic evaluation of aripiprazole plus ADT versus quetiapine (primary analysis) and other AAPs (secondary analysis) plus ADT for the population in the approved indication. The model consisted of four health states: major depressive episode (MDE), remission, symptom-free state, and death. The MDE state is characterized by a depressed mood (most of the day, nearly every day) and/or markedly diminished interest or pleasure in all, or almost all, activities (most of the day, nearly every day).[5,9-12] "Remission" is defined according to each of the randomized controlled trials (RCTs) included in the manufacturer's ITC. The definition varies substantially across the studies, with remission based on Hamilton Depression Rating Scale (HAM-D) score, various Montgomery–Åsberg Depression Rating Scale (MADRS) score cut-offs, and MADRS score cut-off as well as 50% reduction in MADRS score (Table 2).[4] "Symptom-free state" was defined as a minimum of nine months of sustained remission.[4]

All patients enter the model in the MDE health state on existing ADT and receive either adjunctive therapy with aripiprazole or with quetiapine (primary and secondary), olanzapine (secondary), or risperidone (secondary). Patients remain in the MDE state for a minimum of six weeks.[4] Patients fulfilling the remission criteria after six weeks transition to the remission health state. If a patient does not fulfil the remission criteria at six weeks, he or she receives a second course of treatment with the same AAP. If the patient does not respond to the second course, the patient remains in the MDE state and is switched to best supportive care. This could involve switching to or augmenting with one of a number of alternative pharmacotherapies (e.g., lithium or triiodothyronine [T3]), or non-pharmacotherapy approaches (e.g., electroconvulsive therapy, psychotherapy, or neurostimulation therapy).[4] In the remission state, patients are maintained on ADT. Patients can transition to the symptom-free health state if remission is maintained for nine months (39 weeks),[4] or to the MDE state in the event of a relapse. In the model, whether an individual patient transitions to remission is determined by randomly drawing a number between 0% and 100%. If the number drawn is less than or equal to the probability of treatment-specific remission at a particular week, then treatment is considered successful at that time and the patient transitions to remission. If the number drawn is greater than the probability for remission (e.g., greater than the cumulative remission rate of 28.8% in the case of aripiprazole), then treatment of the patient is considered unsuccessful at achieving remission and the patient remains in the MDE health state to receive a second six week course of treatment with the same AAP. During each MDE, the model assumed a maximum of two AAP courses per patient, and it assumed that each patient could have more than one MDE. Time spent in the remission and symptom-free health states is dependent upon the number of prior MDEs.[4] Patients in the symptom-free health state transition back to the MDE in the event of a relapse. At any point in the model, a patient can transition to the death health state. These health states are summarized in Figure 1.

The use of a patient-level simulation assists in simulating highly heterogeneous patient populations, chronic disease with recurring events, and diseases in which timing of events is highly variable and dependent on prior history. The model primarily uses beta and gamma distributions for the sampling of data.

FIGURE 1: STRUCTURE OF PATIENT-LEVEL SIMULATION



Source: Manufacturer-submitted pharmacoeconomic report, page 37, Figure 4-4.

2.2 Clinical Inputs

2.2.1 Efficacy

The baseline characteristics of patients in the patient-level discrete event simulation were drawn from the three RCTs comparing aripiprazole plus ADT to placebo plus ADT, and the results were pooled using an inverse variance weighted method.[4]

Efficacy data included in the manufacturer's economic model were based on an ITC, using Bayesian meta-analytic techniques, of aripiprazole, quetiapine, olanzapine, and risperidone. Measurement scales and criteria used to define remission were inconsistent across studies included in the ITC (Table 2). A random-effects model was chosen to compare the studies, using a vague prior; to obtain odds ratios of adjunctive aripiprazole versus adjunctive treatment with the other defined AAPs. For the economic evaluation, the odds ratios from the ITC for the AAPs versus aripiprazole were applied to the pooled remission rates for aripiprazole augmentation in order to calculate the relative remission rate for the comparator treatment options. [redacted] (Table 2). CADTH Common Drug Review (CDR) identified two potential sources of bias that could affect the relative effectiveness among the four interventions; these were baseline disease severity and the definition of remission. The included studies for risperidone and aripiprazole had an average MADRS score of 26 at baseline, and they defined remission as a MADRS score ≤ 10. However, studies for quetiapine and olanzapine had higher baseline MADRS scores, 28 and 30, respectively, and they defined remission as MADRS score ≤ 8. These biases systematically showed that quetiapine and olanzapine were less effective than risperidone and aripiprazole because studies for the former interventions included patients with more severe MDD and used a more conservative remission definition than aripiprazole and risperidone studies. The ITC model did not adjust for these biases, and the true relative efficacy among the four interventions could not be confirmed.

TABLE 2: ODDS RATIOS OF REMISSION RATES OBTAINED FROM MAJOR DEPRESSIVE DISORDER INTERVENTIONS VERSUS ARIPIPRAZOLE

Number of Studies/Number of Patients	Average Baseline Depression Severity (Average MADRS Score)	Definition of Remission	Remission Rate (Comparator Versus Aripiprazole) OR (95% CI)	Rank by Relative Efficacy[a]
Risperidone				
[redacted]				
Aripiprazole				
[redacted]				
Quetiapine				
[redacted]				
Olanzapine				
[redacted]				

CI = confidence interval; MADRS = Montgomery–Åsberg Depression Rating Scale; OR = odds ratio.
[a] Based on odds ratios reported in the network meta-analysis provided by the manufacturer.[4]
Source: Manufacturer-submitted pharmacoeconomic report (page 30 and 33).

2.2.2 Risk of subsequent events

The model assumed that the probability of having a future MDE was proportional to the number of previous MDEs. According to the submitted model, this assumption was based on a 10 year retrospective cohort of 318 patients;[13] the study reported that the risk of recurrence increased by 16% for each successive episode of major depression (Table 3). However, the submitted economic model used transition probabilities different from those reported in the cohort study,[13] and this discrepancy was not explained or justified. Because the economic model applied these transition rates in similar way to all interventions, it was unlikely that this discrepancy would affect the relative cost-effectiveness ratios between comparators. The model also assumed that time spent in the "remission" and "symptom-free" health states was dependent upon the number of prior MDEs.[4]

TABLE 3: DISEASE PROGRESSION IN FUNCTION OF PAST MAJOR DEPRESSIVE EPISODES

	Probability of Subsequent MDE (%)	Incremental Risk Increase With Each Successive MDE (%)	
Number of previous MDEs	As used in the model[a]	Based on the probabilities used in the model	Based on Solomon et al.[13]
1	27		16
2	46	19	32
3	53	7	48
4	56	3	64
5	71	15	80

MDE = major depressive episode.
[a] Source: Manufacturer-submitted pharmacoeconomic submission.

2.2.3 Harms

Adverse events (AEs) were not included in the model, as data regarding the long-term impact of treatment with AAPs on AEs were not available, and AEs occurring over the six week duration of the clinical trials were assumed to be relatively minor in terms of their impact on quality of life and costs.

However, the manufacturer also stated that all AAPs used as augmenting drugs are associated with AEs; therefore, the side effect profile should be taken into consideration. There was a significant difference between risperidone and other AAPs, including a prolactin increase (seen in 80% to 90% of female patients). Elevated prolactin levels are associated with a number of adverse outcomes, including delayed sexual maturation, menstrual irregularities, decreased testosterone levels and sperm mobility, gynecomastia, galactorrhea, sexual dysfunction, decreased bone mass density, and osteoporosis. Aripiprazole has little impact (if not a decrease) on prolactin levels and is associated with improvement in some domains of sexual functioning (e.g., interest in sex and sexual satisfaction).[14-16] Sedation is common class effect of AAPs; however, the manufacturer stated this was a prominent side effect of quetiapine treatment, while aripiprazole can quickly restore patient functioning and alertness.[4,17,18]

2.2.4 Mortality

Death could occur for patients at any time in the model, with all-cause mortality data being taken from Statistics Canada. Although death by suicide was not included as an outcome in the model, the model used literature-based suicide rates among patients experiencing an MDE to adjust mortality rates.

2.2.5 Costs

Direct health care costs were used in the model according to health state and applied on a per-week basis.

Health care utilization and costs for the MDE health state were taken from a retrospective population-based study from Quebec, based on information from the database of the Régie de l'assurance maladie du Québec.[4] The manufacturer did note that information regarding the history of depression and number of MDEs for patients was not available; therefore, the generalizability of the information to this population is unclear. However, the manufacturer indicated that the results from Monfared et al.[19] likely represented a conservative estimate, as patients included in the clinical trials on which the submitted economic evaluation is based had to have failed to respond to at least two courses of ADT during the current MDE.

The manufacturer indicated that there were no Canadian studies that assessed utilization and costs in the remission health state. The manufacturer included data from a Swedish observational, naturalistic study[20] that assessed the impact of remission versus non-remission to inform the remission health state. However, this study was very small (56 patients), and the majority of patients had moderate MDD at study inclusion. Sobocki et al.[20] found that total direct costs for patients in remission were 37% less than for patients without remission. Thus, the manufacturer applied this proportion to the cost of MDE from Monfared et al.[19] to estimate a six month cost of $1,522.49 for the remission health state (adjusted to a weekly cost of $35.34). The assumption of generalizability of the results from 56 patients in Sweden to the Canadian population is associated with considerable uncertainty.

The manufacturer assumed that patients in the symptom-free state remained on ADT but consumed no other related health care resources.

The manufacturer indicated that no information was available to inform a reasonable estimate of cost and resource use for best supportive care (BSC) in the model, and, as these costs were not expected to vary based on prior treatment, no cost was assumed for BSC in the model.

2.2.6 Drug costs

AAP costs used in the economic evaluation were from the 2013 Ontario Drug Benefit Formulary (ODBF) database, with the exception of the cost of aripiprazole. Generic pricing was used when available. The prices of aripiprazole supplied by the manufacturer were substantially lower than the price of aripiprazole listed in the ODBF. According to the submitted model, the mean dose of AAPs was determined based on the respective RCTs included in the ITC. CDR noticed that the cost used for quetiapine was based on the price of 300 mg per day tablets; however, quetiapine can be used in a range of 150 mg per day to 300 mg per day for the treatment of MDE. Therefore, the model might have overestimated the cost for quetiapine. Furthermore, the model assumed that quetiapine would be used as adjunctive treatment with ADT drugs; however, the approved product monograph did not specify whether quetiapine should be used as monotherapy or add-on treatment for MDE. A Canadian practice guideline has recommended its use either as monotherapy or add-on, with higher-level evidence supporting its use as monotherapy.[5] This assumption overestimated the costs associated with quetiapine for the treatment of MDE.

The costs of the various ADT drugs in the economic evaluation are from the ODBF as well; however, an overall cost of ADT is weighted based on the frequency of use of each of these ADTs from the aripiprazole trials. CDR noticed that using weighted ADT cost based on trial observations might not be an accurate representation of the full spectrum of ADT available in different jurisdictions. The model assumed patients were receiving the highest recommended dose of the ADT in costing ADT.

2.2.7 Utilities

The manufacturer undertook a literature search to identify utility data to inform the health states of MDE, remission, and symptom-free states in the model. The manufacturer identified several studies, each of which employed different measurement tools to elicit the utility values.[21-26] The patient populations were also stated to differ significantly; thus, the utility values differed substantially among the studies.

The manufacturer used utility values from Schaffer et al.[21] to inform the health state utilities for the base-case analysis. Schaffer et al. used the standard gamble technique to measure the utility scores for patients with current depression (n = 19), with past depression (n = 21), and healthy controls (n = 35).[21] The reported utility score was 0.51 for a current mild depressive episode and 0.82 for a past depressive episode, regardless of its severity.[21]

2.2.8 Time horizon

The manufacturer presented the results of the economic evaluation using a lifetime time horizon, which was supported by the CADTH economic evaluation guidelines,[8] given the chronic and relapsing nature of MDD. However, although lifetime horizon was stated in the submitted pharmacoeconomic report, the actual length of time horizon was not stated in the manufacturer's pharmacoeconomic report. The submitted model, however, appeared to use a duration of 999 years; this time horizon is not a realistic expectation for a patient's lifetime.

2.2.9 Discounting

In accordance with the Canadian guidelines for the economic evaluation of health technologies, costs and effects were discounted at 5% per annum.[8] Sensitivity analyses were carried out using discount rates of 0% and 3% for both costs and effects to investigate the impact of discounting on the results of the analyses.

3. RESULTS

3.1 Manufacturer's Base Case

In the manufacturer's base-case analysis using the results of 500,000 patient simulations, the following results were found:

- The incremental costs and QALYs for aripiprazole versus BSC are $98 and 0.020, respectively, leading to an incremental cost per QALY gained of $4,829.

TABLE 4: SUMMARY OF RESULTS OF THE MANUFACTURER'S BASE CASE: ARIPIPRAZOLE VERSUS QUETIAPINE

	Total Costs ($)	Incremental Cost of Aripiprazole ($)	Total QALYs	Incremental QALYs of Aripiprazole	Incremental Cost per QALY ($)
Aripiprazole	30,457		10.54		
Quetiapine	30,359	98	10.52	0.020	4,829

QALY = quality-adjusted life-year.

Given the limitations of some of the parameter estimates used in the model, as detailed above, the base-case analysis is not appropriate.

3.2 Summary of the Manufacturer's Sensitivity Analyses

3.2.1 Scenario analysis: aripiprazole versus quetiapine, olanzapine, and risperidone

The results of the comparison are presented on a "Tornado diagram" (Figure 2).

The results showed that risperidone was more effective and less costly compared with aripiprazole, quetiapine, and olanzapine, dominating these treatments in the CUA. The results of the analysis were driven by higher remission rates and lower drug acquisition costs for risperidone compared with the other AAPs included in the analysis.

TABLE 5: SUMMARY OF RESULTS OF THE MANUFACTURER'S BASE CASE: ARIPIPRAZOLE VERSUS QUETIAPINE, OLANZAPINE, AND RISPERIDONE

	Total Costs ($)	Incremental Cost Versus Comparator ($)	Total QALYs	Incremental QALYs Versus Comparator	Incremental Cost per QALY ($)
Risperidone	29,803		10.58		
Quetiapine	30,359	556	10.52	–0.06	Dominated by risperidone
Aripiprazole	30,457	654	10.54	–0.04	Dominated by risperidone
Olanzapine	30,464	661	10.50	–0.08	Dominated by risperidone

QALY = quality-adjusted life-year.

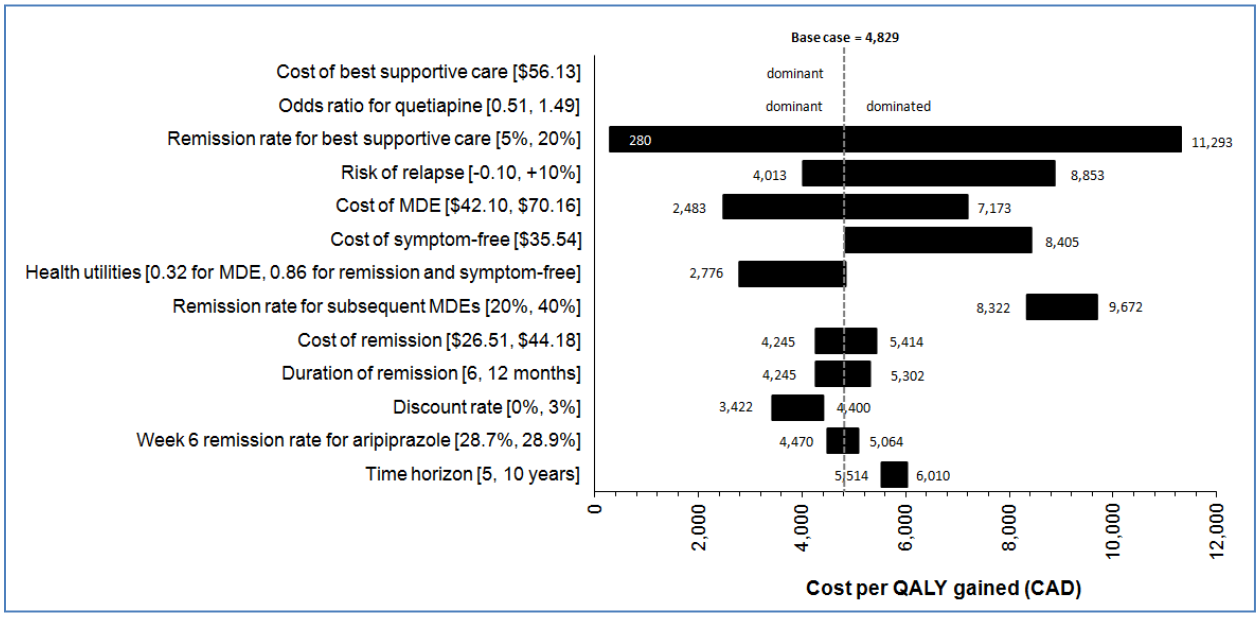
The absence of direct evidence comparing the efficacy of AAPs in the treatment of resistant MDD means the comparative efficacy data were based on an ITC conducted for quetiapine, olanzapine, and risperidone versus aripiprazole, which was subject to several limitations (Appendix 7 of the CDR Clinical Report).

3.2.2 One-way sensitivity analyses

Sensitivity analyses were conducted on time horizon, duration of remission, efficacy of remission for aripiprazole, comparative efficacy for quetiapine, efficacy of remission for subsequent MDEs, remission rate for BSC, time to relapse, cost of MDE, cost of remission, cost of symptom-free status, cost of ADT, cost of BSC, discount rate, and health utilities (MDE, remission, and symptom-free states).

Figure 2 presents the univariate sensitivity analyses conducted and their results. In two of the 13 analyses, aripiprazole dominates quetiapine. In 10 analyses, the ICUR for aripiprazole versus quetiapine ranged from $280 to $11,293. In one analysis, however, aripiprazole was dominated by quetiapine (upper confidence interval odds ratio for quetiapine). Overall, the analyses suggested that aripiprazole was more cost-effective than quetiapine given current threshold values of a QALY; however, the model was sensitive to the comparative efficacy of aripiprazole and quetiapine.

FIGURE 2: RESULTS FOR THE SENSITIVITY ANALYSIS



CAD = Canadian dollars; MDE = major depressive episode; QALY = quality-adjusted life-year.
Source: Manufacturer-submitted pharmacoeconomic submission, page 55, Figure 5-1.

3.2.3 Probabilistic sensitivity analysis

The manufacturer conducted a cost-effectiveness acceptability analysis to test the impact of uncertainty around the comparative effectiveness. The analysis showed that there was a 59% chance that aripiprazole would be cost-effective at a willingness to pay of $20,000 per QALY gained. The chance that aripiprazole was cost-effective compared with quetiapine increased to 64% at a willingness to pay of $50,000 per QALY gained.

3.3 CADTH Common Drug Review Analyses

CDR analyses were conducted in order to evaluate uncertainties about the quetiapine dose that was used in the model, the potential use of quetiapine as monotherapy, and the length of the lifetime horizon. CDR also evaluated ICUR versus price reduction based on the most likely scenario.

Using quetiapine in a range from 150 mg to 300 mg per day instead of 300 mg per day only increased the ICUR of aripiprazole from $1,799 to $6,977 as compared with quetiapine (Table 6).

Using quetiapine as monotherapy would reduce the cost of background ADT; ICUR of aripiprazole, compared with quetiapine, increased from $1,799 to $6,211 or $7,593 when assuming that 50% or 100% of patients were using quetiapine as monotherapy (Table 6).

The submitted model used an extremely long lifetime horizon of 999 years. CDR tested shorter lifetime horizons of 30 years, 40 years, and 55 years; these values were based mainly on the starting age used in the model (45 years). The associated ICURs of aripiprazole, compared with quetiapine, were $4,990, $4,678, and $5,156 with lifetime horizons of 30 years, 40 years, and 55 years, respectively (Table 6).

TABLE 6: CADTH COMMON DRUG REVIEW REANALYSIS OF INCREMENTAL COST-UTILITY RATIOS FOR ARIPIPRAZOLE VERSUS COMPARATORS

	Total Costs ($)	Incremental Cost of Aripiprazole ($)	Total QALYs	Incremental QALYs of Aripiprazole	Incremental Cost per QALY of Aripiprazole
Manufacturer's base-case analysis					
Aripiprazole	30,456		10.53		
Quetiapine	30,359	97	10.51	0.020	$4,829
Analysis based on a range of quetiapine doses[a]					
Aripiprazole	30,456		10.53		
Quetiapine	30,316	140	10.51	0.020	$6,977
Assuming that 100% of patients would use quetiapine as monotherapy					
Aripiprazole	30,456		10.53		
Quetiapine	30,303	153	10.51	0.020	$7,593
Assuming that 50% of patients would use quetiapine as monotherapy					
Aripiprazole	30,456		10.53		
Quetiapine	30,331	125	10.51	0.020	$6,211
Assuming a time horizon of 30 years					
Aripiprazole	28,170		9.76		
Quetiapine	28,070	100	9.74	0.020	4,990
Assuming a time horizon of 40 years					
Aripiprazole	30,017		10.39		
Quetiapine	29,923	94	10.37	0.020	$4,678
Assuming a time horizon of 55 years					
Aripiprazole	30,445		10.53		
Quetiapine	30,341	104	10.51	0.020	$5,156
Based on "most likely scenario"[b]					
Aripiprazole	30,007		10.39		
Quetiapine	29,852	165	10.37	0.020	$8,231

QALY = quality-adjusted life-year.

[a] Assuming that 33% of the patients will use 150 mg per day, 33% will use 200 mg per day, and 34% will use 300 mg per day.

[b] Assuming a range of quetiapine doses, 50% of patients using quetiapine as monotherapy, and a 40-year time horizon.

Table 7 summarizes ICURs of aripiprazole compared with quetiapine resulting from different price-reduction scenarios. For example, a 40% price reduction would reduce the ICUR from 4,829 to 207; aripiprazole would become dominant over quetiapine when the price is reduced by 50%.

TABLE 7: CADTH COMMON DRUG REVIEW ANALYSIS OF INCREMENTAL COST-UTILITY RATIOS BASED ON VARIOUS PRICE-REDUCTION SCENARIOS

Scenario	ICUR Based on Manufacturer's Analysis (Versus Quetiapine) ($)	Revised ICUR Based on CDR "Most Likely Scenario" (Versus Quetiapine) ($)
Manufacturer's base case	4,829	8,231
10% price reduction	2,837	6,225
20% price reduction	846	4,219
30% price reduction	Dominant	2,213
40% price reduction		207
50% price reduction		Dominant
60% price reduction		
70% price reduction		
80% price reduction		

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio.

4. DISCUSSION

The key limitations associated with the manufacturer's submission are summarized in Table 8.

The submitted economic evaluation was based on the comparative effectiveness of aripiprazole versus quetiapine, risperidone, and olanzapine obtained from the ITC provided by the manufacturer. The ITC contained several limitations that hindered the interpretability of results. The impact of uncertainty around the comparative effectiveness, in terms of remission, was partially evaluated in a sensitivity analysis conducted by the manufacturer, which reported that aripiprazole would be dominated by quetiapine when the upper efficacy limit of quetiapine versus aripiprazole was considered.

Another limitation of the economic evaluation was that it considered that quetiapine would be used at 300 mg per day; however, the product monograph for quetiapine indicates that it can be used in a range from 150 mg per day to 300 mg per day for the treatment of an MDE.[5,6] Furthermore, the model assumed that quetiapine would be used as adjunctive therapy only; however, quetiapine could be used as monotherapy or add-on, with higher-level evidence supporting its use as monotherapy.[5] Therefore, the model seemed to overestimate the costs associated with quetiapine, which results in an underestimation of the ICUR for aripiprazole versus quetiapine.

Length of lifetime horizon was not specified in the submitted pharmacoeconomic report; however, the submitted model indicated a time horizon of 999 years. While it is uncertain whether this is total life-years (which for a model of 500,000 patients is very small), this value is extremely high if it is the actual expected lifetime of the patient, and results in an underestimation of the ICUR for aripiprazole versus quetiapine. The model assumed a starting age of 45 years for the simulated patients; thus, a 40-year lifetime horizon would be an appropriate length, assuming a life expectancy of 85 years. Based on this assumption, CDR estimate of ICUR of aripiprazole compared with quetiapine was $4,678 instead of $4,829.

TABLE 8: KEY LIMITATIONS OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Parameter / Assumption	Issue	Impact
Comparative efficacy is uncertain	Remission odds ratio for aripiprazole compared with quetiapine was 0.87 (95% CI, 0.51 to 1.49)	Based on the remission odds ratio; ICUR for aripiprazole compared with quetiapine ranged from dominant to dominated by quetiapine.
Inappropriate use of comparator	The model assumed that quetiapine would be used at 300 mg/d; however, quetiapine can be used in a range of 150 mg to 300 mg/d for the treatment of MDE.	The model underestimated the cost-effectiveness. CDR estimate of ICUR is $3,472 as opposed to the manufacturer's base case of $1,799.[a]
	The model assumed that quetiapine would be used as adjunctive treatment with ADT drugs; however, it can be used either as monotherapy or add-on	The model underestimated the cost-effectiveness. CDR estimate of ICUR is $2,875[b] as opposed to the manufacturer's base case of $1,799.[a]
Inappropriate lifetime horizon length	The submitted model used lifetime horizon of 999 years.	Based on a more appropriate time horizon to represent the lifetime, the model appears to have underestimated the cost-effectiveness. CDR estimate of ICUR is $4,678[c] as opposed to the manufacturer's base case of $4,829.[a]

ADT = antidepressant therapy; CDR = CADTH Common Drug Review; CI = confidence interval; ICUR = incremental cost-utility ratio; MDE = major depressive episode.
[a] All other variables were not changed.
[b] Assuming that 50% of patients would use quetiapine as monotherapy.
[c] Assuming a lifetime horizon of 40 years.

4.1 Issues for Consideration

The available evidence showed that aripiprazole did not differ, with statistical significance, from quetiapine in terms of remission rate, and the numerical difference between the two comparators generated a minimal difference in terms of QALYs (0.020). This difference might not be sufficient to justify the price difference between aripiprazole and quetiapine.

In Canada, two AAP drugs were approved for MDE treatment, quetiapine and aripiprazole. Olanzapine and risperidone are two other AAP drugs that are available in Canada but are not indicated by Health Canada for the treatment of MDE. The manufacturer's analysis showed that risperidone dominated quetiapine, aripiprazole, and olanzapine.

The model assumed that patients would use ADT during the MDE and remission episodes. The specific ADT options and their use percentage were based on observations from aripiprazole clinical trials (Table 9); however, the different jurisdictions might vary in terms of the availability and use of these medications, and that would limit the generalizability of ADT cost estimates.

TABLE 9: ANTIDEPRESSANT THERAPY USED IN ARIPIPRAZOLE CLINICAL TRIALS

ADT	Average usage in aripiprazole clinical trials (%)
Escitalopram 10 mg = 20 mg citalopram	32.05
Fluoxetine	16.00
Paroxetine	4.75
Sertraline	14.65
Venlafaxine	27.50

ADT = antidepressant therapy.

4.2 Patient Input

Mood Disorders Society of Canada (MDSC) is a national voluntary consumer/patient-controlled health charity, which hosts a national online discussion forum containing more than 18,000 posts from persons with mental illness and their families and caregivers. MDSC collected information from personal histories of key MDSC staff living with depression/MDD and a literature review to provide input for the aripiprazole submission.

Patients reported:

- A loss of interest in the pleasures of life, work, family, and friends; inability to concentrate and make decisions; feeling negative, anxious, trapped, unable to act, despair, guilty, and unworthy; fatigue, an overall loss of energy, and bodily pain. Patients may express suicidal thoughts and plans. The most common symptoms experienced by Canadians include lack of motivation, loss of ability to enjoy favourite activities, difficulty concentrating, and feelings of isolation. Some of these aspects were captured within the domains of the health-related quality of life assessment tool used and reported in the manufacturer's economic evaluation.
- The patient group reported that the burden of this disease is also felt by caregivers. The manufacturer did not undertake a sensitivity analysis from the societal perspective, and did not include caregiver burden in the model or report.
- Sometimes current therapies become less effective for patients on a long-term basis, and they therefore need access to newer medications to maintain control of their illness.
- Side effects were not explicitly reported in the manufacturer's economic evaluation, but are part of the scores used to determine severity of the condition (e.g., HAM-D).

5. CONCLUSIONS

Based on the results of the manufacturer's indirect treatment comparison, the efficacy of aripiprazole and quetiapine appear similar, which would render aripiprazole more costly than quetiapine. There is, however, considerable uncertainty around the magnitude and direction of the numerical differences. CDR identified several limitations in the manufacturer's analysis, which, when adjusted for in the model, resulted in an incremental cost per QALY gained of $8,231 for aripiprazole versus quetiapine.

APPENDIX 1: COST COMPARISON TABLE FOR DRUGS FOR MAJOR DEPRESSIVE DISORDER

Clinical experts have deemed the comparators presented in Table 10 and Table 11 to be appropriate. 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.

TABLE 10: COST COMPARISON TABLE FOR MAJOR DEPRESSIVE DISORDER

Drug/ Comparator	Strength (mg)	Dosage Form	Price ($)	Recommended Daily Dose (mg)	Average Daily Cost ($)	Average Annual Cost ($)
Atypical antipsychotics						
Aripiprazole (Abilify)	**2** **5** **10** **15** **20** **30**	**Tablet**	**3.0013**[a] **3.3783**[a] **3.8933**[a] **3.8933**[a] **3.8933**[a] **3.8933**[a]	**2 to 15**	**3.00 to 3.89**	**1,095 to 1,421**
Quetiapine extended release (Seroquel XR)	50 150 200 300 400	ER tablet	0.3950 0.7780 1.0520 1.5440 2.0960	50 to 300	0.40 to 1.54	144 to 564
Serotonin-norepinephrine reuptake inhibitors						
Desvenlafaxine (Pristiq)	50 100	Tablet	2.9738[b]	50 to 100	2.97	1,085
Duloxetine (Cymbalta)	30 60	DR capsule	1.8914 3.7893	60	3.79	1,383
Venlafaxine Extended release (generic)	37.5 75 150	ER capsule	0.1643 0.3285 0.3469	75 to 225	0.33 to 0.68	120 to 247
Selective serotonin reuptake inhibitors						
Citalopram[c] (generics)	20 40	Tablet	0.3329	20 to 60	0.33 to 0.67	122 to 243
Escitalopram (Cipralex)	10 20	Tablet	1.7270 1.8387	10 to 20	1.73 to 1.84	630 to 671
	10 20	OD tablet	1.6933 1.8027		1.70 to 1.80	618 to 658
Fluoxetine (generics)	10 20	Capsule	0.8650[d] 0.4598	20 to 60	0.46 to 1.38	168 to 503
Fluvoxamine[c] (generics)	50 100	Tablet	0.2105 0.3783	100 to 300	0.76 to 2.27	276 to 828
Paroxetine (generics)	10 20 30	Tablet	0.5612[d] 0.4514 0.4796	20 to 50	0.45 to 0.93	165 to 340
Sertraline[c] (generics)	25 50 100	Capsule	0.2038 0.4000 0.4458	50 to 200	0.40 to 0.89	146 to 325

Drug/ Comparator	Strength (mg)	Dosage Form	Price ($)	Recommended Daily Dose (mg)	Average Daily Cost ($)	Average Annual Cost ($)
Norepinephrine-dopamine reuptake inhibitors						
Bupropion (generics)	100 150	SR tablet	0.1547 0.2298	100 to 150	0.15 to 0.23	56 to 84
	150 300	ER tablet	0.3982 0.7963	150 to 300	0.40 to 0.80	145 to 291
Alpha 2-adrenergic agonist						
Mirtazapine[c] (generics)	15 30 45	Tablet	0.2018[d] 0.3100 0.6053[d]	15 to 45	0.20 to 0.61	74 to 221
	15 30 45	OD tablet	0.0975 0.1950 0.2925		0.10 to 0.30	36 to 107
Reversible monoamine oxidase inhibitor						
Moclobemide[c] (generics)	100 150 300	Tablet	0.2520 0.1515 0.2974	300 to 600	0.30 to 0.59	109 to 217

DR = delayed release; ER = extended release; OD = orally disintegrating; SR = sustained release; XR = extended release.
Source: Ontario Drug Benefit Formulary (February 2014) unless otherwise indicated.
[a] Manufacturer's submitted price.
[b] McKesson Canada wholesale price (February 2014).
[c] Indicated for "depressive illness."
[d] Saskatchewan Formulary (February 2014).

TABLE 11: ATYPICAL ANTIPSYCHOTICS USED FOR MAJOR DEPRESSIVE DISORDER WITHOUT INDICATION

Drug/ Comparator	Strength (mg)	Dosage Form	Price ($)	Recommended Daily Dose (mg)	Average Daily Cost ($)	Average Annual Cost ($)
Olanzapine (generics)	2.5 5 7.5 10 15 20	Tablet	0.4493 0.8986 1.3479 1.7972 2.6958 10.3093[a]	7.5 to 10	1.35 to 1.80	492 to 656
	5 10 15 20	OD tablet	0.8937 1.7857 2.6777 5.9377[a]		1.34 to 1.79	489 to 652
Risperidone (generics)	0.25 0.5 1 2 3 4	Tablet	0.1314 0.2202 0.3041 0.6071 0.9108 1.2144	1 to 3	0.30 to 0.91	111 to 332
	1 2 3 4	OD tablet	0.5150 1.0188 2.2913 3.0638		0.52 to 2.29	188 to 836

OD = orally disintegrating.
Prices are from the Ontario Drug Benefit Formulary (February 2014) unless otherwise indicated.
[a] McKesson wholesale pricing (May 2014).

APPENDIX 2: SUMMARY OF KEY OUTCOMES

TABLE 12: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS ARIPIPRAZOLE RELATIVE TO QUETIAPINE?

Aripiprazole Versus quetiapine	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)				X		
Drug treatment costs alone				X		
Clinical outcomes		X				
Quality of life		X[a]				
Incremental cost-effectiveness ratio or net benefit calculation	$8,231					

NA = not applicable.
[a] Based on quality-adjusted life-years.
Note: The above is based on CADTH Common Drug Review reanalysis.

TABLE 13: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS ARIPIPRAZOLE RELATIVE TO RISPERIDONE AND OLANZAPINE?

	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Aripiprazole versus risperidone						
Costs (total)				X		
Drug treatment costs alone					X	
Clinical outcomes				X		
Quality of life				X[a]		
Incremental cost-effectiveness ratio or net benefit calculation	Dominated by risperidone					
Aripiprazole versus olanzapine						
Costs (total)		X				
Drug treatment costs alone					X	
Clinical outcomes		X				
Quality of life		X[a]				
Incremental cost-effectiveness ratio or net benefit calculation	Aripiprazole is dominant					

NA = not applicable.
[a] Based on quality-adjusted life-years.
Note: The above is based on the manufacturer's analysis.

APPENDIX 3: ADDITIONAL INFORMATION

TABLE 14: 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 15: AUTHOR INFORMATION

Authors	Affiliations
Lisa Bernard Melissa Thompson	Cornerstone Research Group Inc.

	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[a]	

[a] Bristol-Myers Squibb Canada retains the rights to publication of all aspects of the current study.

REFERENCES

1. Bristol-Myers Squibb Canada cover letter accompanying CDR submission package for Abilify for major depressive disorder [**CONFIDENTIAL** manufacturer's letter]. Saint-Laurent (QC): Bristol-Myers Squibb Canada; 2013 Sep 30.
2. CEDAC final recommendation: Aripiprazole - request for advice (Abilify - Bristol-Myers Squibb Canada). Indication: Schizophrenia and related pyschotic disorders [Internet]. Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH); 2011 Jul 18. [cited 2014 May 2]. Available from: http://www.cadth.ca/media/cdr/complete/cdr_complete_Abilify_July-20-2011_e.pdf
3. CEDAC final recommendation: Aripiprazole (Abilify - Bristol-Myers Squibb Canada). Indication: Schizophrenia and related pyschotic disorders [Internet]. Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH); 2010 Apr 27. [cited 2014 May 2]. Available from: http://www.cadth.ca/media/cdr/complete/cdr_complete_Abilify_April-30-2010_e.pdf
4. Pharmacoeconomic evaluation. In: CDR submission: Abilify (aripiprazole) tablets. Company: Bristol-Myers Squibb Canada. [**CONFIDENTIAL** manufacturer's submission]. St.Laurent (QC): Bristol-Myers Squibb Canada; 2013 Sep.
5. Kennedy SH, Milev R, Giacobbe P, Ramasubbu R, Lam RW, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) Clinical guidelines for the management of major depressive disorder in adults. IV. Neurostimulation therapies. J Affect Disord. 2009 Oct;117 Suppl 1:S44-S53.
6. [Pr]Seroquel XR® quetiapine fumarate extended-release tablets, 50,150,200, 300 and 400 mg quetiapine (as quetiapine furmarate). Antipyschotic/antidepressant agent [product monograph]. Mississauga (ON): AstraZeneca Canada Inc.; 2013 Dec 20.
7. Anderson IM, Haddad PM. CANMAT guidelines for depression: clear and user-friendly. J Affect Disord. 2009 Oct;117 Suppl 1:S3-S4.
8. Canadian Agency for Drugs and Technologies in Health. Guidelines for the economic evaluation of health technologies: Canada [Internet]. 3rd ed. Ottawa: The Agency; 2006 Mar. [cited 2014 Apr 17]. Available from: http://www.cadth.ca/media/pdf/186_EconomicGuidelines_e.pdf
9. Kennedy SH, Lam RW, Parikh SV, Patten SB, Ravindran AV. Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults. Introduction. J Affect Disord. 2009 Oct;117 Suppl 1:S1-S2.
10. Patten SB, Kennedy SH, Lam RW, O'Donovan C, Filteau MJ, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults. I. Classification, burden and principles of management. J Affect Disord. 2009 Oct;117 Suppl 1:S5-14.
11. Parikh SV, Segal ZV, Grigoriadis S, Ravindran AV, Kennedy SH, Lam RW, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults. II. Psychotherapy alone or in combination with antidepressant medication. J Affect Disord. 2009 Oct;117 Suppl 1:S15-S25.
12. Ravindran AV, Lam RW, Filteau MJ, Lesperance F, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) Clinical guidelines for the management of major depressive disorder in adults. V. Complementary and alternative medicine treatments. J Affect Disord. 2009 Oct;117 Suppl 1:S54-S64.

13. Solomon DA, Keller MB, Leon AC, Mueller TI, Lavori PW, Shea MT, et al. Multiple recurrences of major depressive disorder. Am J Psychiatry [Internet]. 2000 Feb [cited 2014 Feb 28];157(2):229-33. Available from: http://ajp.psychiatryonline.org/data/Journals/AJP/3709/229.pdf

14. Berman RM, Fava M, Thase ME, Trivedi MH, Swanink R, McQuade RD, et al. Aripiprazole augmentation in major depressive disorder: a double-blind, placebo-controlled study in patients with inadequate response to antidepressants. CNS Spectr. 2009 Apr;14(4):197-206.

15. Berman RM, Thase ME, Trivedi MH, Hazel JA, Marler SV, McQuade RD, et al. Long-term safety and tolerability of open-label aripiprazole augmentation of antidepressant therapy in major depressive disorder. Neuropsychiatr Dis Treat [Internet]. 2011 [cited 2014 Apr 22];7:303-12. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3104689

16. Jing Y, Kalsekar I, Curkendall SM, Carls GS, Bagalman E, Forbes RA, et al. Intent-to-treat analysis of health care expenditures of patients treated with atypical antipsychotics as adjunctive therapy in depression. Clin Ther. 2011 Sep;33(9):1246-57.

17. Wright BM, Eiland EH, III, Lorenz R. Augmentation with atypical antipsychotics for depression: a review of evidence-based support from the medical literature. Pharmacotherapy. 2013 Mar;33(3):344-59.

18. Miller DD. Atypical antipsychotics: sleep, sedation, and efficacy. Prim Care Companion J Clin Psychiatry [Internet]. 2004 [cited 2014 Apr 22];6(Suppl 2):3-7. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC487011

19. Monfared AA, Han D, Sheehy O, Bexton B, LeLorier J. Assessment of Canadian provincial expenditures in depressed patients treated with venlafaxine XR versus SSRIs: the APEX Study. Curr Med Res Opin. 2006;22(1):83-94.

20. Sobocki P, Ekman M, Agren H, Runeson B, Jonsson B. The mission is remission: health economic consequences of achieving full remission with antidepressant treatment for depression. Int J Clin Pract. 2006 Jul;60(7):791-8.

21. Schaffer A, Levitt AJ, Hershkop SK, Oh P, MacDonald C, Lanctot K. Utility scores of symptom profiles in major depression. Psychiatry Res. 2002 Jun 1;110(2):189-97.

22. Revicki DA, Wood M. Patient-assigned health state utilities for depression-related outcomes: differences by depression severity and antidepressant medications. J Affect Disord. 1998 Feb;48(1):25-36.

23. Bennett KJ, Torrance GW, Boyle MH, Guscott R. Cost-utility analysis in depression: the McSad utility measure for depression health states. Psychiatr Serv [Internet]. 2000 Sep [cited 2014 Mar 7];51(9):1171-6. Available from: http://ps.psychiatryonline.org/data/Journals/PSS/3551/1171.pdf

24. Bennett KJ, Torrance GW, Boyle MH, Guscott R, Moran LA. Development and testing of a utility measure for major, unipolar depression (McSad). Qual Life Res. 2000 Feb;9(1):109-20.

25. Supina AL, Johnson JA, Patten SB, Williams JV, Maxwell CJ. The usefulness of the EQ-5D in differentiating among persons with major depressive episode and anxiety. Qual Life Res. 2007 Jun;16(5):749-54.

26. Patten SB, Williams JV, Lavorato DH, Bulloch AG, Currie G, Emery H. Depression and painful conditions: patterns of association with health status and health utility ratings in the general population. Qual Life Res. 2014 Feb;23(1):363-71.