



Common Drug Review

Pharmacoeconomic Review Report

February 2017

Drug	Aripiprazole prolonged release suspension for injection (ABILIFY MAINTENA) (300 mg and 400 mg vial)
Indication	For the maintenance treatment of schizophrenia in stabilized adult patients.
Listing request	For the treatment of schizophrenia in patients judged to be at risk of nonadherence, or who demonstrate: <ul style="list-style-type: none">• inadequate disease control or significant adverse events from one or more oral antipsychotic medications, or• inadequate disease control or significant adverse events from one or more conventional long-acting injectable antipsychotic agents
Manufacturer	Otsuka Canada Pharmaceutical Inc. & Lundbeck Canada Inc.

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in psychiatry who provided input on the conduct of the review and the interpretation of findings.

Aripiprazole prolonged release injectable suspension (Abilify Maintena) CADTH Common Drug Review Pharmacoeconomic Report was prepared using PharmaStat data from IMS Health Canada Inc. The analyses, conclusions, opinions and statements expressed are those of the Canadian Agency for Drugs and Technologies in Health and not those of IMS Health Canada Inc.

Through the CADTH Common Drug Review (CDR) process, CADTH undertakes reviews of drug submissions, resubmissions, and requests for advice, and provides formulary listing recommendations to all Canadian publicly funded federal, provincial, and territorial drug plans, with the exception of Quebec.

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TABLE OF CONTENTS

ABBREVIATIONS	ii
SUMMARY	iii
REVIEW OF THE PHARMACOECONOMIC SUBMISSION	1
1. Introduction.....	2
2. Summary of Pharmacoeconomic Submission	5
3. Key Limitations	8
4. Issues for Consideration	10
5. Conclusions.....	11
APPENDIX 1: CADTH COMMON DRUG REVIEW REANALYSIS OF FREQUENCY OF ADMINISTRATION OF PALIPERIDONE AND RISPERIDONE LAI.....	12
APPENDIX 2: PRICE REDUCTION SCENARIOS.....	13
REFERENCES	14

Tables

Table 1: Cost Comparison Table of Antipsychotics for Schizophrenia.....	2
Table 2: Manufacturer’s Base-Case Results — Two-Year Discounted Costs of Long-Acting Injectable Atypical Antipsychotics	5
Table 3: Manufacturer’s “Real-World” Multivariate Analysis Results.....	6
Table 4: Manufacturer’s Calculations and Inputs for “Real-World” Multivariate Analysis	6
Table 5: Manufacturer’s Base Case With Updated (September 2014) Ontario Drug Benefit List Prices	9
Table 6: Manufacturer’s “Real-World” Multivariate Analysis with Updated (September 2014) ODB List Prices	9
Table 7: Comparison of Manufacturer’s and CDR’s “Real-World” Multivariate Analysis Results	10
Table 8: CADTH Common Drug Review’s “Real-World” Multivariate Analysis Calculations and Inputs.....	12
Table 9: Average Price of Paliperidone Based on Utilization Data	13
Table 10: Additional Cost (Savings) per Dose with Aripiprazole Long-Acting Injectable Versus Paliperidone Long-Acting Injectable at Various Price Reduction Scenarios.....	13

ABBREVIATIONS

AAP	atypical antipsychotic
IM	intramuscular
LAI	long-acting injectable
NMA	network meta-analysis
ODB	Ontario Drug Benefit

SUMMARY

Aripiprazole prolonged release injectable suspension (Abilify Maintena) is a long-acting injectable (LAI) atypical antipsychotic (AAP) indicated for the maintenance treatment of schizophrenia in stabilized adult patients. The recommended starting and maintenance dose of aripiprazole LAI is 400 mg monthly (administered no sooner than 26 days after the previous injection). If there are adverse reactions with the 400 mg dosage, reduction of the dose to 300 mg once monthly should be considered. At the submitted price of \$456.18 per 300 mg or 400 mg single-use vial, the average cost of aripiprazole LAI is \$16.29 per day when administered intramuscularly every four weeks (28 days).

The manufacturer submitted a cost-minimization analysis comparing aripiprazole LAI (300 mg or 400 mg every four weeks) to paliperidone LAI (50 mg, 75 mg, 100 mg, or 150 mg every four weeks) and risperidone LAI (12.5 mg, 25 mg, 37.5 mg, or 50 mg every two weeks) in adult patients with schizophrenia over a two-year time horizon from the perspective of a Canadian health ministry with the second-year costs discounted at 5%. The assumption of similar clinical efficacy, safety, and tolerability was based on a manufacturer-funded, unpublished network meta-analysis (NMA) that compared aripiprazole LAI to risperidone LAI, paliperidone LAI, olanzapine LAI, haloperidol LAI, oral risperidone, and oral aripiprazole. Costs included in the analysis were for drug costs, loading regimens costs (additional oral AAPs or higher LAI dose administered at initiation of LAI therapy to achieve therapeutic levels), and administration costs (physician service and pharmacy dispensing fees).

In the manufacturer's base case, which used product monograph-recommended doses, loading regimens, and frequency of administration, the two-year discounted cost of aripiprazole LAI 400 mg (\$12,651) was \$945 less than paliperidone LAI 75 mg (\$13,596) and \$1,687 less expensive than risperidone LAI 37.5 mg (\$14,338). These results were robust to a variety of sensitivity analyses, including a "real-world" multivariate analysis that used utilization data from IMS Brogan PharmaStat and US data to estimate the relative costs of the comparators when used as in clinical practice. The "real-world" analysis found the two-year discounted cost of aripiprazole LAI (\$12,696) to be \$5,767 less expensive than paliperidone LAI (\$18,463) and \$3,929 less expensive than risperidone LAI (\$16,625).

The CADTH Common Drug Review (CDR) identified a number of key limitations in the manufacturer's analysis, including:

- Uncertainty in the clinical similarity and dose equivalency of aripiprazole LAI to paliperidone LAI or risperidone LAI
- Absence of oral AAPs as comparators given the indicated population of stable patients
- Uncertainty in the assumptions and data sources used in the "real-world" multivariate sensitivity analysis.

At the submitted price, aripiprazole LAI costs substantially more than both oral antipsychotics — including oral aripiprazole (daily cost: \$4.13 to \$4.88) — and long-acting typical antipsychotics. When compared with other available long-acting injectable atypical antipsychotics, and when loading regimens and administration costs are considered, based on utilization data, aripiprazole LAI could generate savings ranging from \$166 to \$6,024 compared with paliperidone LAI, and savings ranging from \$820 to \$4,071 compared with risperidone LAI over two years. The clinical similarity of aripiprazole LAI to paliperidone LAI and risperidone LAI is uncertain due to limitations in the manufacturer's NMA, as well as the fact that doses used in clinical practice appeared somewhat higher than those used in clinical trials included in the NMA.

REVIEW OF THE PHARMACOECONOMIC SUBMISSION

Aripiprazole prolonged release injectable suspension (Abilify Maintena) is a long-acting injectable (LAI) atypical antipsychotic (AAP) indicated for the maintenance treatment of schizophrenia in stabilized adult patients.¹ The recommended starting and maintenance dose of aripiprazole LAI is 400 mg monthly (administered no sooner than 26 days after the previous injection). If there are adverse reactions with the 400 mg dosage, reduction of the dose to 300 mg once monthly should be considered.¹ The submitted price is \$456.18 per 300 mg or 400 mg single-use vial, or \$16.29 per day when administered intramuscularly every four weeks.

After the first aripiprazole LAI injection, treatment should be continued with 10 mg to 20 mg oral aripiprazole for 14 consecutive days to maintain therapeutic antipsychotic concentrations during initiation of therapy (loading regimen).¹

The manufacturer is requesting a listing for the treatment of schizophrenia in patients judged to be at risk of nonadherence, or who demonstrate inadequate disease control or significant adverse events from one or more oral antipsychotic medications; or who demonstrate inadequate disease control or significant adverse events from one or more conventional LAI antipsychotic agents.²

1. INTRODUCTION

1.1 Cost Comparison Table

Clinical experts have deemed the comparator treatments presented in Table 1 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. Existing Product Listing Agreements are not reflected in the table and as such may not represent the actual costs to public drug plans.

TABLE 1: COST COMPARISON TABLE OF ANTIPSYCHOTICS FOR SCHIZOPHRENIA

Comparator Drug	Strength	Dosage Form	Price (\$)	Recommended Daily Dose	Daily Drug Cost (\$)	Annual Drug Cost (\$)
Long-Acting Atypical Antipsychotics						
Aripiprazole (Abilify Maintena)	300 mg 400 mg	Vial for injection	456.1800 ^a	400 mg IM once monthly	16.29 ^b	5,947
Paliperidone (Invega Sustenna)	50 mg 75 mg 100 mg 150 mg	Vial for injection	317.9100 476.8700 476.8700 635.8300	75 mg IM once monthly	17.03 ^b	6,216
Risperidone (Risperdal Consta)	12.5 mg 25 mg 37.5 mg 50 mg	Vial for injection	78.5900 ^c 163.1700 244.7500 326.3400	25 to 50 mg IM every 2 weeks	11.66 to 23.31	4,254 to 8,508
Long-Acting Typical Antipsychotics						
Flupentixol decanoate (Fluanxol Depot)	20 mg/1 mL 100 mg/1 mL	vial for injection	7.4016 37.0079	20 mg to 40 mg IM every 2 to 3 weeks	0.35 to 1.06	128 to 386
Fluphenazine decanoate (Modecate)	100 mg/1 mL	vial for injection	29.7800	12.5 mg to 50 mg IM every 2 to 3 weeks	1.42 to 2.13	518 to 776
Haloperidol decanoate (generic)	50 mg/1 mL 100 mg/1 mL 250 mg/5 mL 500 mg/5 mL	vial for injection	8.4640 ^d 11.6648 30.2500 58.3240	50 mg to 300 mg IM every four weeks	0.30 to 1.25	110 to 456
Pipotiazine palmitate	25 mg/1 mL 50 mg/1 mL 100 mg/2 mL	vial for injection	16.4400 27.8800 53.0200	75 mg to 150 mg IM every 4 weeks	1.58 to 2.89	577 to 1,055
Zuclopenthixol decanoate (Clopixol Depot)	200 mg /1 mL	vial for injection	15.0482 ^d	150 mg to 300 mg IM every 2 to 4 weeks	0.54 to 2.15	196 to 785
Oral Atypical Antipsychotics						
Asenapine (Saphris)	5 mg 10 mg	tab	1.5516 ^e	5 mg twice daily	3.10	1,133

CDR PHARMACOECONOMIC REVIEW REPORT FOR ABILIFY MAINTENA

Comparator Drug	Strength	Dosage Form	Price (\$)	Recommended Daily Dose	Daily Drug Cost (\$)	Annual Drug Cost (\$)
Aripiprazole (Abilify)	2 mg	tab	3.1267	10 mg to 15 mg daily	4.13 to 4.88	1,509 to 1,781
	5 mg		3.5216			
	10 mg		4.1337			
	15 mg		4.8784			
	20 mg		5.5937			
	30 mg		6.9284			
Clozapine (generic)	25 mg	tab	0.6594 ^d	150 mg to 600 mg daily	3.96 to 15.87	1,447 to 5,792
	100 mg		2.6446 ^d			
Lurasidone (Latuda)	40 mg	tab	4.0800	40 mg to 120 mg daily	4.08	1,489
	80 mg					
	120 mg					
Olanzapine (generic)	2.5 mg	tab	0.4493	5 mg to 20 mg daily	0.90 to 3.59	328 to 1,312
	5 mg		0.8986			
	7.5 mg		1.3479			
	10 mg		1.7972			
	15 mg		2.6958			
	5 mg	ODT	0.8937		0.89 to 3.57	326 to 1,304
Paliperidone (Invega)	3 mg	XR tab	3.7240	6 mg once daily	5.57	2,033
	6 mg		5.5700			
	9 mg		7.4240			
Quetiapine (generic)	25 mg	tab	0.1235	150 mg to 300 mg twice daily	1.15 to 1.93	421 to 705
	100 mg		0.3295			
	150 mg		1.6465 ^d			
	200 mg		0.6617			
	300 mg		0.9656			
	50 mg	XR tab	0.3950	400 mg to 800 mg once daily	2.10 to 4.19	765 to 1,530
	150 mg		0.7780			
	200 mg		1.0520			
300 mg	1.5440					
400 mg	2.0960					
Risperidone (generic)	0.25 mg	tab	0.1314	4 mg to 6 mg daily	1.21 to 1.82	443 to 665
	0.5 mg		0.2202			
	1 mg		0.3041			
	2 mg		0.6071			
	3 mg		0.9108			
	4 mg		1.2144			
	0.5 mg	ODT	0.5588	4 mg to 6 mg daily	2.04 to 3.06	746 to 1,117
	1 mg		0.5150			
	2 mg		1.0188			
	3 mg		1.5275			
4 mg	2.0425					

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Comparator Drug	Strength	Dosage Form	Price (\$)	Recommended Daily Dose	Daily Drug Cost (\$)	Annual Drug Cost (\$)
Ziprasidone (Zeldox)	20 mg	cap	1.7665	40 mg to 80 mg twice daily	4.05	1,477
	40 mg		2.0233			
	60 mg		2.0233			
	80 mg		2.0233			

cap = capsule; IM = intramuscular; mg = milligram; ODT = oral disintegrating tablet; XR = extended release.

Note: All prices are from the Ontario Drug Benefit (ODB) Formulary (Sept 2014) unless otherwise indicated. Administration and loading regimen costs are not included.

^a Manufacturer's submitted price.

^b Daily drug cost calculated assuming "monthly" injections are given every 28 days, consistent with the manufacturer's assumptions and confirmed via consultation with a clinical expert.

^c Saskatchewan Formulary (Sept 2014).

^d Alberta Formulary (Sept 2014).

^e Asenapine is indicated for schizophrenia, but is only reimbursed by public plans for bipolar disorder. Therefore, the McKesson Canada pricing (including markup, Sept 2014) is provided in the table, rather than public formulary prices.

2. SUMMARY OF PHARMACOECONOMIC SUBMISSION

The manufacturer submitted a cost-minimization analysis comparing aripiprazole LAI (300 mg or 400 mg every four weeks) to paliperidone LAI (50 mg, 75 mg, 100 mg, or 150 mg every four weeks) and risperidone LAI (12.5 mg, 25 mg, 37.5 mg, or 50 mg every two weeks) in adult patients with schizophrenia over a two-year time horizon from the perspective of a Canadian health ministry, with the second-year costs discounted at 5%. Costs included in the analysis were drug costs, loading regimens costs (additional oral AAPs or higher LAI dose administered at initiation of LAI therapy to achieve therapeutic levels), and administration costs (physician service and pharmacy dispensing fees).

The assumption of similar clinical efficacy, safety, and tolerability was based on a manufacturer-funded, unpublished network meta-analysis (NMA) that compared aripiprazole LAI with risperidone LAI, paliperidone LAI, olanzapine LAI, haloperidol LAI, oral risperidone, and oral aripiprazole.

The manufacturer's base-case analysis used product monograph–recommended doses, loading regimens, and frequency of administration for aripiprazole LAI, paliperidone LAI, and risperidone LAI.^{1,3,4} The assumed dose distribution for each LAI AAP was as follows:

- Aripiprazole LAI: 90% of patients would receive 400 mg monthly and 10% would receive 300 mg monthly
- Paliperidone LAI: 100% of patients would receive 75 mg monthly
- Risperidone LAI: 100% of patients would receive 37.5 mg every two weeks.

The two-year discounted cost of aripiprazole LAI 400 mg (\$12,651) was \$945 less expensive than paliperidone LAI 75 mg (\$13,596) and \$1,687 less expensive than risperidone LAI 37.5 mg (\$14,338).

TABLE 2: MANUFACTURER'S BASE-CASE RESULTS — TWO-YEAR DISCOUNTED COSTS OF LONG-ACTING INJECTABLE ATYPICAL ANTIPSYCHOTICS

Comparator	Treatment Costs	Loading Regimen Costs ^a	Administration Costs ^b	Total Discounted Costs	Incremental Cost
Aripiprazole LAI 400 mg or 300 mg	\$11,578	\$67	\$1,006	\$12,651	Reference
Paliperidone LAI 75 mg	\$11,925	\$626	\$1,045 ^c	\$13,596	\$945
Risperidone LAI 37.5 mg	\$12,301	\$26	\$2,011	\$14,338	\$1,687

LAI = long-acting injectable.

^a Loading regimen consisted of 14 days of administration with 15 mg per day of oral aripiprazole after aripiprazole LAI was started, or 21 days of overlap with 4 mg per day of oral risperidone, or a 150 mg loading dose of paliperidone LAI, with initiation of regular dosing schedule seven days later.

^b Administration costs include a \$31 physician fee (Ontario Schedule of Benefits for Physician Services) and an \$8.62 pharmacy dispensing fee per visit or per dose.

^c Aripiprazole and paliperidone LAI are both administered monthly, but the total administration cost is higher with paliperidone due to the loading dose.

Source: Adapted from manufacturer's submission, Table 5.1.i, page 23. Dosing, frequency, and loading regimen as per product monographs.⁵

These results were robust to a variety of sensitivity analyses, the most applicable of which was a “real-world” multivariate analysis using utilization data from IMS Brogan PharmaStat and US data to estimate the relative costs of the comparators when used as in clinical practice.

Of note, the CADTH Common Drug Review (CDR) was able to replicate the dose distributions used by the manufacturer using 2013 PharmaStat data from IMS Health Canada Inc. (see Table 8 in Appendix 1). Based on the manufacturer and CDR reanalysis, the average doses of risperidone LAI and paliperidone LAI were approximately 40 mg and 115 mg, respectively (using Ontario public drug programs as a reference and without differentiating indications), which is higher than the dose used in the manufacturer’s base case, especially for paliperidone LAI.

This “real-world” analysis (see Table 3) found the two-year discounted cost of aripiprazole LAI (\$12,696) to be \$5,767 less expensive than paliperidone LAI (\$18,463) and \$3,929 less expensive than risperidone LAI (\$16,625). Much of the increase in the relative costs of paliperidone LAI and risperidone LAI compared with the base case is due to the distribution of patients across the various doses, the manufacturer’s estimation of frequency of administration (see Table 4), and the assumption of extended oral supplementation with risperidone during risperidone LAI initiation (104 days versus 21).

TABLE 3: MANUFACTURER’S “REAL-WORLD” MULTIVARIATE ANALYSIS RESULTS

Comparator	Treatment Costs	Loading Regimen Costs	Administration Costs	Total Discounted Costs	Incremental Cost
Aripiprazole LAI	\$11,620	\$67	\$1,009	\$12,696	Reference
Paliperidone LAI	\$16,556	\$626	\$1,281	\$18,463	\$5,767
Risperidone LAI	\$14,299	\$126	\$2,200	\$16,625	\$3,929

LAI = long-acting injectable.

Source: Adapted from manufacturer’s economic submission, Table 5.2.ii, page 27, and accompanying Microsoft Excel economic model.⁵

TABLE 4: MANUFACTURER’S CALCULATIONS AND INPUTS FOR “REAL-WORLD” MULTIVARIATE ANALYSIS

Comparator	Q3 2013 Dose Distribution ^a	Q3 2013 Days	Q3 2013 Units	Q3 2013 Days/Unit	Frequency of Administration (Weeks) ^b
Paliperidone LAI 50 mg	6%	13,734	570	24.09	3.44
Paliperidone LAI 75 mg	13%	27,700	1,174	23.59	3.37
Paliperidone LAI 100 mg	39%	80,063	3,504	22.85	3.26
Paliperidone LAI 150 mg	42%	81,831	3,717	22.02	3.15
Risperidone LAI 25 mg	28%	64,864	4,888	13.27	1.90
Risperidone LAI 37.5 mg	26%	57,431	4,684	12.26	1.75
Risperidone LAI 50 mg	46%	102,044	7,968	12.81	1.83

CDR PHARMACOECONOMIC REVIEW REPORT FOR ABILIFY MAINTENA

Comparator	Q3 2013 Dose Distribution ^a	Q3 2013 Days	Q3 2013 Units	Q3 2013 Days/Unit	Frequency of Administration (Weeks) ^b
Aripiprazole LAI 300 mg	20%	N/A	N/A	N/A	3.99 ^c
Aripiprazole LAI 400 mg	80%	N/A	N/A	N/A	3.99 ^c

LAI = long-acting injectable.

^a Dose distributions for risperidone LAI and paliperidone LAI are based on the number of claims for each dose divided by the total number of claims for each LAI. Aripiprazole LAI dose distribution was based on US data on file with the manufacturer, which does not affect the results of the analyses due to flat pricing across doses.

^b Example of calculation for paliperidone LAI 50 mg: $\text{days/units}/7 = 12,734/570/7 = 3.44$.

^c Aripiprazole LAI frequency estimated from US administration data, "Lundbeck Data on File, Nov 2013."

Source: Manufacturer's economic submission, Table 4.11.i, page 18, and Table 4.11.vi, page 22. All data extracted from IMS Brogan PharmaStat Ontario Public Database for Q3 2013 unless otherwise indicated.⁵

3. KEY LIMITATIONS

Clinical similarity to other LAIs uncertain

As there are no head-to-head trials available comparing aripiprazole LAI with risperidone LAI or paliperidone LAI, the manufacturer submitted an NMA that incorporated data from trials including the three LAIs available in Canada as well as olanzapine LAI, haloperidol LAI, oral aripiprazole, and olanzapine.⁶ While generally well conducted, the NMA suffered from a weakly linked network, the “lumping” of all included therapeutic doses of comparators together, the “lumping” of sub-therapeutic doses into the placebo arm, and the unexplained exclusion of trials that might have strengthened the network and/or validated the results (e.g., placebo-controlled risperidone LAI trials). Given the uncertainty in the equivalence of dosing among treatments in the NMA, it is unclear whether there is clinical similarity among treatments. As a result, uncertainty exists in both the base-case and the “real-world” analyses.

The utilization analysis performed by both the manufacturer and CDR yielded a weighted-average dose for paliperidone LAI of approximately 115 mg, which differs from the weighted-average dose of approximately 83 mg in the paliperidone LAI study⁷ included in the NMA.

Additionally, the comparative effectiveness of LAI AAPs in the specific population of patients who are at risk of nonadherence or who have inadequate control while on oral AAPs or long-acting typical antipsychotics (i.e., the situations relevant to the manufacturer’s requested listing criteria) has not been established.

Key comparators omitted

As the indication for aripiprazole LAI is for stable patients with schizophrenia, the oral AAPs, particularly oral aripiprazole, could be considered as economic comparators. A clinical trial⁸ found that aripiprazole LAI was as effective as oral aripiprazole in the maintenance treatment of adult patients with schizophrenia stabilized on oral aripiprazole. With an assumption of clinical similarity, aripiprazole LAI costs approximately \$16.29 a day when administered every four weeks, compared with a usual cost of between \$4.13 and \$4.88 per day for oral aripiprazole. Thus, aripiprazole LAI would cost approximately \$4,166 to \$4,438 more per patient per year, not including oral dose titrations or LAI protocol initiations.

Updated comparator pricing available

Since the manufacturer performed its analyses, the ODB formulary list prices for many AAPs have increased slightly, making the relative cost of aripiprazole LAI somewhat less expensive versus its comparators (see Table 5Table 5 and Table 6).

TABLE 5: MANUFACTURER’S BASE CASE WITH UPDATED (SEPTEMBER 2014) ONTARIO DRUG BENEFIT LIST PRICES

Comparator	Treatment Costs	Protocol Initiation Costs	Administration Costs	Total Discounted Costs	Incremental Cost
Aripiprazole LAI 400 mg or 300 mg	\$11,578	\$68	\$1,006	\$12,652	Reference
Paliperidone LAI 75 mg	\$12,103	\$636	\$1,045	\$13,784	\$1,132
Risperidone LAI 37.5 mg	\$12,424	\$26	\$2,011	\$14,461	\$1,809

LAI = long-acting injectable.

TABLE 6: MANUFACTURER’S “REAL-WORLD” MULTIVARIATE ANALYSIS WITH UPDATED (SEPTEMBER 2014) ODB LIST PRICES

Comparator	Treatment Costs	Protocol Initiation Costs	Administration Costs	Total Discounted Costs	Incremental Cost
Aripiprazole LAI	\$11,620	\$68	\$1,009	\$12,697	Reference
Paliperidone LAI	\$16,804	\$636	\$1,281	\$18,721	\$6,024
Risperidone LAI	\$14,442	\$126	\$2,200	\$16,768	\$4,071

LAI = long-acting injectable; ODB = Ontario Drug Benefit.

“Real-world” multivariate assumptions and sources

There were concerns regarding the assumptions made in the manufacturer’s “real-world” multivariate analysis, including uncertainty in the method used to calculate the frequency of administration of risperidone LAI and paliperidone LAI comparators in clinical practice, as well as the different and unclearly defined data sources provided for the frequency of aripiprazole LAI use. However, these assumptions did not affect the results of the base case.

The manufacturer used the number of days and number of units claimed to calculate usage frequency from the Q3 2013 Ontario public drug plan data set (IMS Brogan, PharmaStat). As a result of patients starting and stopping, unclear accuracy of pharmacy-reported data for days claimed, etc., it is likely that this method overestimates the frequency of administration for paliperidone LAI and risperidone LAI. The clinical expert consulted by CDR considered it improbable that patients were regularly receiving LAI injections at increased frequency rather than decreased. CDR conducted a reanalysis using units per person over the 92 days of Q3 2013 (see Table 8 in Appendix 1). While this method might underestimate the frequency of administration in clinical practice, when combined with the manufacturer’s method of frequency calculation, it yields a more plausible range of “real-world” relative costs.

Additionally, the manufacturer used US data of unknown source to estimate aripiprazole LAI administration frequency without providing the data set. While Canadian utilization data on aripiprazole LAI are not yet available, without the corresponding US data on paliperidone LAI and risperidone LAI utilization, nor the details of the data collected (geography, timeline, payer, etc.), it is impossible to judge the comparability and thus the suitability of the US information. Given the significant differences

between health care systems in the two countries, it is unlikely the two sources of data are compatible. Instead, CDR calculated the relative two-year “real-world” discounted costs when aripiprazole was used at the frequency recommended in the product monograph (every 4.00 weeks), as well as at the Q3 2013 dose market share weighted-average frequency of paliperidone LAI (4.82 weeks) under the assumption that aripiprazole LAI would be used as infrequently in clinical practice as paliperidone, given their identical recommended frequencies (Table 7).

TABLE 7: COMPARISON OF MANUFACTURER’S AND CDR’S “REAL-WORLD” MULTIVARIATE ANALYSIS RESULTS

Comparator	Manufacturer’s Assumptions		CDR’s Two Alternate Assumptions			
	Total Cost (Days/Unit Frequency Method)	Incremental Cost (Day/Unit Frequency Method)	Total Cost (Units/Person Method Ari q4.00w)	Incremental Cost (Units/Person Method Ari q4.00w)	Total Cost (Units/Person Method Ari q4.82w)	Incremental Cost (Units/Person Method Ari q4.82w)
Aripiprazole LAI	\$12,697	Reference	\$12,651	Reference	\$10,510	Reference
Paliperidone LAI	\$18,721	\$6,024	\$12,817	\$166	\$12,817	\$2,307
Risperidone LAI	\$16,768	\$4,071	\$13,471	\$820	\$13,471	\$2,961

Ari = aripiprazole LAI; CDR = CADTH Common Drug Review; q4.00w = administered every 4.00 weeks (product monograph–recommended frequency); q4.82w = administered every 4.82 weeks (weighted-average paliperidone frequency).

When used together as a plausible range, the manufacturer’s and CDR’s “real-world” sensitivity analyses yield a two-year discounted cost range for aripiprazole LAI of \$10,510 to \$12,697, making it \$166 to \$6,024 less expensive than paliperidone LAI (\$12,817 to \$18,721) and \$820 to \$4,071 less expensive than risperidone LAI (\$13,471 to \$16,768). (See Table 7.)

4. ISSUES FOR CONSIDERATION

- Patient input identified a preference for long-acting medications. Some patients reported increased adherence to their medication and better contact with their physician when using aripiprazole LAI as part of a clinical trial or compassionate supply. Additionally, patients emphasized the individual variability of response to antipsychotics with respect to both effectiveness in lessening symptoms as well as tolerance of side effects. Patients indicated a strong preference for the availability of multiple therapeutic options due to this variation.
- In order to assess the impact of potential changes or variability in pricing, CDR conducted an additional analysis considering the relative cost per dose of aripiprazole LAI compared with paliperidone LAI in various price reduction scenarios for both products (Appendix 2).

5. CONCLUSIONS

At the submitted price, aripiprazole LAI costs substantially more than both oral antipsychotics, including oral aripiprazole (daily cost: \$4.13 to \$4.88), as well as long-acting typical antipsychotics. When compared with other available long-acting injectable atypical antipsychotics, and when loading regimens and administration costs are considered, based on utilization data, aripiprazole LAI could generate savings ranging from \$166 to \$6,024 when compared with paliperidone LAI, and savings ranging from \$820 to \$4,071 when compared with risperidone LAI over two years. The clinical similarity of aripiprazole LAI with paliperidone LAI and risperidone LAI is uncertain due to limitations in the manufacturer's NMA and to the fact that doses used in clinical practice appeared somewhat higher than those used in clinical trials included in the NMA.

APPENDIX 1: CADTH COMMON DRUG REVIEW REANALYSIS OF FREQUENCY OF ADMINISTRATION OF PALIPERIDONE AND RISPERIDONE LAI

TABLE 8: CADTH COMMON DRUG REVIEW'S "REAL-WORLD" MULTIVARIATE ANALYSIS CALCULATIONS AND INPUTS

Comparator	Q3 2013 Dose Distribution ^a	Q3 2013 Units ^a	Q3 2013 Persons ^a	Q3 2013 Units/Person	Frequency of Administration (Weeks) ^a
Paliperidone LAI 50 mg	6%	570	214	2.66	4.93
Paliperidone LAI 75 mg	13%	1,174	452	2.60	5.06
Paliperidone LAI 100 mg	39%	3,504	1,321	2.65	4.95
Paliperidone LAI 150 mg	42%	3,721	1,305	2.85	4.61
Risperidone LAI 25 mg	28%	4,888	936	5.22	2.52
Risperidone LAI 37.5 mg	26%	4,684	806	5.81	2.26
Risperidone LAI 50 mg	46%	7,968	1,335	5.97	2.20
Aripiprazole LAI 300 mg	20%	N/A	N/A	N/A	4.00 or 4.82 ^c
Aripiprazole LAI 400 mg	80%	N/A	N/A	N/A	4.00 or 4.82 ^c

LAI = long-acting injectable.

^a Q3 2013 units and persons extracted from IMS Brogan PharmaStat Ontario Public Database. Dose market share estimations are unchanged from the manufacturer's analysis.

^b Example of calculation for paliperidone LAI 50 mg: (# weeks in quarter)/(units/person) = (92/7)/(570/214) = 4.93 week frequency.

^c In the absence of frequency data established as being compatible with that of the comparators, aripiprazole LAI frequency was assumed to be either the product monograph-recommended frequency, or at the same dose market share weighted-average frequency of paliperidone LAI.

APPENDIX 2: PRICE REDUCTION SCENARIOS

In order to assess the impact of potential changes or variability in pricing, the CADTH Common Drug Review (CDR) conducted an additional analysis considering the relative cost per dose of aripiprazole LAI compared with paliperidone LAI in various price reduction scenarios for both products. Only drug costs were considered. The price of paliperidone LAI was based on utilization data from PharmaStat.

TABLE 9: AVERAGE PRICE OF PALIPERIDONE BASED ON UTILIZATION DATA

	Q3 2013 Dose Distribution ^a	ODB List Price (\$)
Paliperidone LAI 50 mg	6%	317.9100
Paliperidone LAI 75 mg	13%	476.8700
Paliperidone LAI 100 mg	39%	476.8700
Paliperidone LAI 150 mg	42%	635.8300
Weighted-average price (\$)		534.10

LAI = long-acting injectable; ODB = Ontario Drug Benefit.

^a Based on PharmaStat Ontario 2013 utilization.

TABLE 10: ADDITIONAL COST (SAVINGS) PER DOSE WITH ARIPIPRAZOLE LONG-ACTING INJECTABLE VERSUS PALIPERIDONE LONG-ACTING INJECTABLE AT VARIOUS PRICE REDUCTION SCENARIOS

		Aripiprazole LAI 300 mg or 400 mg (per Dose)			
		Submitted Price: \$456.18	5% Reduction: \$433.37	10% Reduction: \$410.56	20% Reduction: \$364.94
Paliperidone LAI Weighted-Average Price per Dose	List Price: \$534.10	(\$77.92)	(\$100.73)	(\$123.54)	(\$169.16)
	5% Reduction: \$507.40	(\$51.22)	(\$74.03)	(\$96.84)	(\$142.46)
	10% Reduction: \$480.69	(\$24.51)	(\$47.32)	(\$70.13)	(\$115.75)
	20% Reduction: \$427.28	\$28.90	\$6.09	(\$16.72)	(\$62.34)

LAI = long-acting injectable; ODB = Ontario Drug Benefit.

Note: Price Source: ODB Formulary (Sept 2014) for paliperidone LAI; manufacturer's confidential price for aripiprazole LAI. Administration, protocol initiation, markups, and dispensing fees not included. Doses are those used in the manufacturer's base-case analysis.

As shown in Table 10, at the submitted price, aripiprazole LAI would remain cost-saving up to a 20% reduction in the price of paliperidone LAI.

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