

CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

BREXPIPRAZOLE (REXULTI)

(Lundbeck Canada Inc. and Otsuka Canada
Pharmaceutical Inc.)

Indication: Treatment of schizophrenia in adults

Service Line: CADTH Common Drug Review
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Abbreviations

AAP	atypical antipsychotic
CDR	CADTH Common Drug Review
ER	extended release
ODB	Ontario Drug Benefit
ODT	oral disintegrating tablet
SGA	second-generation antipsychotic
XR	extended release

Drug	Brexpiprazole (Rexulti)
Indication	Treatment of schizophrenia in adults
Reimbursement Request	As per indication
Dosage Form(s)	0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg tablets
NOC Date	February 16, 2017
Manufacturer	Lundbeck Canada Inc. and Otsuka Canada Pharmaceutical Inc.

Summary

Background

Brexpiprazole (Rexulti) is an oral atypical antipsychotic (AAP) drug indicated for the treatment of schizophrenia in adults.¹ It is available as a 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg tablet at a flat price of \$3.50 per tablet, or \$3.50 per day at the recommended dosage of 2 mg to 4 mg daily. According to the product monograph for brexpiprazole, a starting dosage of 1 mg daily is recommended on days 1 to 4, followed by titration to a 2 mg daily dosage on days 5 to 7; daily dose may be increased to 4 mg on day 8 according to the patient's clinical response and tolerability. The maximum recommended daily dose is 4 mg for most patients. The manufacturer is seeking reimbursement of brexpiprazole for the treatment of schizophrenia in adults, as per the Health Canada-approved indication.²

Summary of the Economic Analysis Submitted by the Manufacturer

The manufacturer submitted a cost comparison of brexpiprazole with other oral AAP drugs for the treatment of adult patients with schizophrenia. Two price comparison scenarios were provided by the manufacturer: one scenario compared brexpiprazole with branded AAP drugs (aripiprazole, lurasidone, and ziprasidone); the other scenario assessed brexpiprazole with all AAP drugs that are publicly funded in Canada for the treatment of schizophrenia. The analysis was conducted over a one-year time horizon from the perspective of the Canadian health care payer. Only drug acquisition costs were considered in the analysis, as other health care costs were assumed to be equivalent. Drug costs were obtained from the ODB Formulary, where available, and derived based on product monograph-recommended dose and frequency of administration. The assumption of clinical efficacy and safety was based on two manufacturer-funded unpublished network meta-analyses, which considered the treatment of acute exacerbations and maintenance therapy in schizophrenia.

The submitted price of brexpiprazole is \$3.50 per tablet regardless of strength. Results of the manufacturer's base-case analysis suggest that brexpiprazole (\$1,278 per year) is cost

saving when compared with aripiprazole (\$1,571 to \$1,854 per year), lurasidone (\$1,571 per year), and ziprasidone (\$1,521 per year), irrespective of dose (Table 4). When considering all oral AAP drugs that are reimbursed by participating public drug plans in Canada for the treatment of schizophrenia, brexpiprazole was more costly than most generic therapies irrespective of dose, including olanzapine (\$233 to \$932 per year), olanzapine oral disintegrating tablet (ODT) (\$235 to \$939 per year), quetiapine (\$254 to \$508 per year) and risperidone (\$444 to \$665 per year), as well as risperidone ODT (\$746 to \$1,116 per year). While brexpiprazole is also more costly than generic quetiapine XR at lower recommended doses, it is less costly than quetiapine XR at higher recommended doses of administration (Table 5).

These results were robust to a variety of sensitivity analyses, including a claims-based analysis which compared the weighted average daily cost of brexpiprazole with the weighted cost of other oral AAP drugs when used in clinical practice. The trends observed in this sensitivity analysis were consistent with those observed in the manufacturer's base case: the annual average weighted daily drug cost of brexpiprazole was higher than that of generic olanzapine, risperidone, and quetiapine, but lower than the cost of branded aripiprazole, lurasidone, paliperidone ER, and ziprasidone.

Key Limitations

CADTH Common Drug Review (CDR) identified one key limitation in the manufacturer's analysis:

Clinical similarity to other oral AAP drugs uncertain: The manufacturer suggests that there are no differences in comparative clinical efficacy between brexpiprazole and other oral AAP drugs based on the two submitted indirect comparisons. While the assumption of similar clinical efficacy is supported by the indirect comparison for the treatment of acute exacerbations in schizophrenia, the clinical similarity of brexpiprazole compared with other oral AAP drugs is uncertain when used as a long-term maintenance treatment. In particular, [REDACTED]

[REDACTED]. The indirect comparisons are further limited by the presence of wide credible intervals associated with the effect estimates for brexpiprazole compared with other oral AAP drugs and a high degree of clinical and methodological heterogeneity; as such, statistically non-significant differences do not necessarily imply treatment equivalence. These limitations, coupled with the absence of head-to-head comparative trials render the assumption of clinical similarity between drugs uncertain.

Issues for Consideration

Impact of drug potency and titration on drug costs: Feedback from the clinical expert consulted by CADTH for this review suggests that brexpiprazole is a highly potent medication with a half-life of 91 hours, requiring approximately 10 to 12 days at the target dose to reach a plateau plasma level.^{3,4} As a result, treatment with brexpiprazole may require slow upward titration by way of smaller dosage increments in order to achieve optimal efficacy, particularly when optimizing treatment within the recommended dose range. The clinical expert noted that the range of available dose strengths for brexpiprazole preserves flexibility in dosage adjustment and response to treatment in the acute phase, as well as the management of possible side effects. This flexibility in titration has important

cost implications. Namely, where upward titration is achieved using increasing dosage strengths of brexpiprazole (e.g., 1 mg tablet on days 1 to 4, 2 x 1 mg tablet on days 5 to 7, 3 x 1 mg tablet on days...), the cost of treatment would increase uniformly with each additional tablet given the flat pricing of brexpiprazole. Further, brexpiprazole tablets are not scored, which reduces the option of using half-tablets. Therefore, cost savings resulting from the use of brexpiprazole in place of more costly brand name drugs may not be realized where there is a need to use multiple, identically priced tablets for optimized treatment of patients with schizophrenia.

Variations in comparator pricing between drug plans: Table 1 compares the submitted price of brexpiprazole to the price of relevant comparators as listed in the ODB Formulary (except for asenapine, for which an alternative price source was used). While there is variation in the pricing of AAP drugs among CDR-participating public drug plans, the use of ODB prices for comparison is conservative as the ODB prices for AAP drugs are among the least expensive, with the exception of aripiprazole and lurasidone. Nonetheless, at the submitted price of \$3.50 per day, brexpiprazole is approximately 15% less expensive than the lowest public plan price for aripiprazole (\$4.01 per 10 or 15 mg tablet, Alberta Health Drug Benefit List, accessed May 2017) and lurasidone (\$4.15 per tablet for all doses, Alberta Health Drug Benefit List, accessed May 2017).

Publicly available list prices may not reflect actual costs to public plans: The actual costs paid by Canadian public drug plans for AAP drugs may be lower than those listed on publicly available formularies.

Treatment of major depressive disorder: Brexpiprazole has been approved for use as an adjunctive therapy to antidepressants for the treatment of major depressive disorder in the US; however, it is not currently approved for that indication in Canada.

Results/Conclusions

If the assumption of clinical similarity holds, at the submitted daily price of \$3.50 per tablet, brexpiprazole (\$1,278 per year) is cost saving when compared with aripiprazole (\$1,571 to \$1,854 per year), lurasidone (\$1,571 per year), and ziprasidone (\$1,521 per year), irrespective of dose. However, brexpiprazole is more costly than generic olanzapine (\$233 to \$932 per year), olanzapine ODT (\$235 to \$939 per year), quetiapine (\$254 to \$508 per year), risperidone (\$444 to \$665 per year), and risperidone ODT (\$746 to \$1,116 per year), irrespective of dose. Where brexpiprazole is used instead of generic AAP drugs, public drug plans would incur additional costs. Whether brexpiprazole is more or less costly than generic quetiapine XR depends on the dose considered and prices within individual public drug plans. A price reduction of 27% to 82% would be required for brexpiprazole to be equivalent to the lowest priced generic AAP drug (olanzapine; \$0.64 to \$2.55).

Given the potency of brexpiprazole, and the potential need to optimize treatment using multiple tablets per day, the cost of treatment with brexpiprazole may exceed \$1,278 in the first year.

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 Antipsychotic Drugs for Schizophrenia

Drug/Comparator	Strength	Dosage Form	Price (\$)	Recommended Dose	Average Daily Drug Cost (\$)	Average Annual Drug Cost (\$)
Brexpiprazole (Rexulti)	0.25 mg 0.5 mg 1 mg 2 mg 3 mg 4 mg	Tab	3.5000^a	2 mg to 4 mg once daily	3.50	1,278
Long-Acting Atypical Antipsychotic Drugs						
Aripiprazole (Abilify Maintena)	300 mg 400 mg	Vial for injection	456.1800	400 mg IM once monthly	16.29 ^b	5,947
Paliperidone (Invega Sustenna)	50 mg/0.5 mL 75 mg/0.75 mL 100 mg/1.0 mL 150 mg/1.5 mL	Pre-filled syringe	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	80.9500 ^c 170.2600 255.3700 340.0500	25 to 50 mg IM every 2 weeks	12.16 to 24.29	4,439 to 8,866
Long-Acting Typical Antipsychotic Drugs						
Flupentixol decanoate (Fluanxol Depot)	20 mg/mL 100 mg/mL	Vial for injection	7.7384 38.6918	20 mg to 40 mg IM every 2 to 3 weeks	0.37 to 1.11	135 to 404
Fluphenazine decanoate (Modecate)	100 mg/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/mL 100 mg/mL	Vial for injection	42.3200 ^c 84.6150	50 mg to 300 mg IM every 4 weeks	1.51 to 9.07	552 to 3,309
Pipotiazine palmitate (Piportil L4)	50 mg/mL	Vial for injection	53.0200 ^d	75 mg to 150 mg IM every 4 weeks	2.84 to 5.68	1,037 to 2,073
Zuclopenthixol decanoate (Clopixol Depot)	200 mg/mL	Vial for injection	15.2589 ^d	150 mg to 300 mg IM every 2 to 4 weeks	0.54 to 2.18	199 to 796

Drug/Comparator	Strength	Dosage Form	Price (\$)	Recommended Dose	Average Daily Drug Cost (\$)	Average Annual Drug Cost (\$)
Oral Atypical Antipsychotic Drugs						
Asenapine (Saphris)	5 mg 10 mg	Tab	1.4935 ^e	5 mg twice daily	2.99	1,090
Aripiprazole (Abilify)	2 mg 5 mg 10 mg 15 mg 20 mg 30 mg	Tab	3.2367 3.6184 4.3017 5.0767 4.0067 4.0067	10 mg to 15 mg once daily	4.30 to 5.08	1,570 to 1,853
Clozapine (generic)	25 mg 100 mg	Tab	0.6594 2.6446	300 mg to 600 mg once daily	7.93 to 15.87	2,896 to 5,792
Lurasidone (Latuda)	40 mg 80 mg 120 mg	Tab	4.3000	40 mg to 120 mg once daily	4.30	1,570
Olanzapine (generic)	2.5 mg 5 mg 7.5 mg 10 mg 15 mg	Tab	0.3189 0.6379 0.9568 1.2758 1.9136	5 mg to 20 mg once daily	0.64 to 2.55	233 to 931
	5 mg 10 mg 15 mg	ODT	0.6434 1.2857 1.9280		0.64 to 2.57	235 to 939
Paliperidone (Invega)	3 mg 6 mg 9 mg	XR tab	3.7870 5.6633 7.5500	6 mg once daily	5.66	2,067
Quetiapine (generic)	25 mg 100 mg 200 mg 300 mg	Tab	0.0889 0.2372 0.4764 0.6953	150 mg to 300 mg twice daily	0.70 to 1.39	254 to 508
	50 mg 150 mg 200 mg 300 mg 400 mg	XR tab	0.3950 0.7780 1.0520 1.5440 2.0960	400 mg to 800 mg once daily	2.10 to 4.19	765 to 1,530
Risperidone (generic)	0.25 mg 0.5 mg 1 mg 2 mg 3 mg 4 mg	Tab	0.1314 0.2202 0.3041 0.6071 0.9108 1.2144	4 mg to 6 mg once daily	1.21 to 1.82	443 to 665
	0.5 mg 1 mg 2 mg 3 mg 4 mg	ODT	0.5588 0.5150 1.0188 1.5275 2.0425	4 mg to 6 mg once daily	2.04 to 3.06	746 to 1,117

Drug/Comparator	Strength	Dosage Form	Price (\$)	Recommended Dose	Average Daily Drug Cost (\$)	Average Annual Drug Cost (\$)
Ziprasidone (Zeldox)	20 mg	Cap	1.8378	40 mg to 80 mg twice daily	4.21	1,537
	40 mg		2.1048			
	60 mg		2.1048			
	80 mg		2.1048			

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

Note: All prices are from the Ontario Drug Benefit Formulary (accessed April 2017), unless otherwise indicated, and do not include dispensing fees.

^a Manufacturer's submitted price.²

^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 (accessed April 2017).⁵

^d Alberta Health Drug Benefit Formulary (accessed March 2017).⁶

^e Asenapine is indicated for schizophrenia, but is only reimbursed by public plans for bipolar disorder. Therefore, the QuintilesIMS DeltaPA wholesale acquisition price (including markup, April 2017) is provided in the table, rather than public formulary prices.⁷

Appendix 1: Price Reduction Analysis

The cost of treatment with brexpiprazole may lead to cost savings or to increased costs within individual public drug plans depending on the relevant comparator and the dose administered. Since brexpiprazole is more costly than most generic AAP drugs in the manufacturer’s base-case analysis, CDR considered the price reduction required compared with the lowest priced generic AAP drug (olanzapine) and with generic risperidone, which was suggested to be the most relevant comparator by the clinical expert consulted by CADTH for this review.

As shown in Table 2, the price of brexpiprazole would need to be reduced by 27% to 82% to be equivalent to the lowest priced generic AAP drug (olanzapine) at upper and lower recommended doses, respectively. Similarly, the price of brexpiprazole would need to be reduced by 48% to 65% to be equivalent to risperidone at upper and lower recommended doses, respectively.

Table 2 CDR Analysis for Two Different Price Reduction Scenarios for Brexpiprazole

Scenario	Current Price	Reduction Needed	Reduced Price of Brexpiprazole	Savings ^a (Min. to Max.)
Price reduction needed to equal lowest cost AAP drug (olanzapine)	\$3.50	27% to 82%	\$0.64 to \$2.55	-\$346 to -\$1,045
Price reduction needed to equal risperidone	\$3.50	48% to 65%	\$1.21 to \$1.82	-\$613 to -\$834

AAP = atypical antipsychotic; CDR = CADTH Common Drug Review; max. = maximum; min. = minimum.

^aSavings per patient per year in comparison with the original submitted price of brexpiprazole.

Appendix 2: Reviewer Worksheets

Table 3: Summary of Manufacturer’s Submission

	Brexpiprazole (Rexulti)
Treatment	Brexpiprazole 2 mg to 4 mg once daily
Comparator(s)	<p>Scenario 1</p> <ul style="list-style-type: none"> • Aripiprazole 10 mg to 15 mg once daily • Lurasidone 40 mg to 120 mg once daily • Ziprasidone 40 mg to 80 mg twice daily <p>Scenario 2</p> <ul style="list-style-type: none"> • Aripiprazole 10 mg to 15 mg once daily • Lurasidone 40 mg to 120 mg once daily • Olanzapine 5 mg to 20 mg once daily • Olanzapine ODT 5 mg to 20 mg once daily • Paliperidone ER 6 mg once daily • Quetiapine 150 mg to 300 mg twice daily • Quetiapine XR 400 mg to 800 mg once daily • Risperidone 4 mg to 6 mg once daily • Risperidone ODT 4 mg to 6 mg once daily • Ziprasidone 40 mg to 80 mg twice daily
Study objective	To conduct an economic analysis of brexpiprazole versus other SGAs funded in Canada for the treatment of schizophrenia.
Type of economic evaluation	Cost comparison
Target population	Adult patients with schizophrenia
Perspective	Canadian health care payer
Outcome(s) considered	Drug costs
Key Data Sources	
Cost	<ul style="list-style-type: none"> • Manufacturer’s submitted price for brexpiprazole • Ontario Drug Benefit Formulary list prices for comparators • ODB dispensing fees and markups excluded in the base-case analysis
Clinical efficacy	Unpublished network meta-analyses for acute ⁸ and long-term ⁹ treatment of schizophrenia
Harms	Unpublished network meta-analyses for acute ⁸ and long-term ⁹ treatment of schizophrenia
Time horizon	One year
Results for base case	<p>Scenario 1</p> <p>At an annual cost of \$1,278.38 per patient, brexpiprazole was the least costly alternative compared with aripiprazole (\$1,571.20 to \$1,854.26), lurasidone (\$1,570.58), and ziprasidone (\$1,520.90).</p> <p>Scenario 2</p> <p>At an annual cost of \$1,278.38 per patient, brexpiprazole was less costly than all branded comparators: aripiprazole (\$1,571.20 to \$1,854.26), lurasidone (\$1,570.58), paliperidone ER (\$2,034.44), and ziprasidone (\$1,520.90). However, the least costly alternative depending on dose considered was olanzapine (\$232.99 to \$931.90) or quetiapine (\$253.96 to \$507.92).</p>

ER = extended release; mg = milligrams; ODB = Ontario Drug Benefit; ODT = oral disintegrating tablet; SGA = second-generation antipsychotic; XR = extended release.
 Source: Manufacturer pharmaco-economic submission²

Manufacturer’s Results

The submitted price of brexpiprazole is \$3.50 per tablet for all available doses. At the submitted price, brexpiprazole (\$1,278 per year) is less expensive than aripiprazole (\$1,571 to \$1,854 per year), lurasidone (\$1,571 per year), and ziprasidone (\$1,521 per year), irrespective of dose (Table 4). Therefore, brexpiprazole would likely generate modest cost savings (\$243 to \$576 annually) where it is used instead of aripiprazole, lurasidone, or ziprasidone. Brexpiprazole was considered in a distinct base-case scenario in comparison with these metabolically neutral AAP drugs, as the timing of its administration in the treatment pathway is likely to be similar to these agents. While paliperidone ER (\$2,035 per year) was not considered within this scenario owing to its negative CDR recommendation, this treatment similarly does not generate cost savings for the Canadian health care payer in comparison with brexpiprazole (Table 5). When considering all oral SGA comparators currently approved in Canada for the treatment of schizophrenia, brexpiprazole is more costly than most generic therapies irrespective of dose, including standard olanzapine (\$233 to \$932 per year), olanzapine ODT (\$235 to \$939 per year), standard quetiapine (\$254 to \$508 per year) and risperidone (\$444 to \$665 per year), as well as risperidone ODT (\$746 to \$1,116 per year) (Table 5). Conversely, generic quetiapine XR is less expensive than brexpiprazole at lower recommended doses and more expensive than brexpiprazole at higher recommended doses of administration (Table 5); therefore, cost savings to the Canadian health care payer relating to generic quetiapine XR depend on the product’s dosage regimen.

It is worth noting that the incremental costs of brexpiprazole presented in Table 4 and Table 5 reflect differences in cost relative to comparators based on ODB Formulary prices; however, the magnitude but not the direction of price differences for individual public plans will vary in accordance with the list prices of various comparators within individual jurisdictions.

Table 4: Manufacturer’s Base-Case Results — Cost Comparison of Brexpiprazole Versus Aripiprazole, Lurasidone and Ziprasidone (Scenario 1)

Treatment	Range of Annual Cost (\$) ^a	Incremental Annual Cost (\$) ^b	
		Lower Recommended Dose	Upper Recommended Dose
Brexpiprazole (Rexulti)	1,278.38	Reference	Reference
Ziprasidone (Zeldox) ^c	1,520.90	242.53	242.53
Lurasidone (Latuda)	1,570.58	292.20	292.20
Aripiprazole (Abilify)	1,571.20 to 1,854.26	292.82	575.89

^a Based on recommended doses. Costs do not include dispensing fees or markups.

^b Positive numbers indicate that the comparator costs more than brexpiprazole. All prices are from the Ontario Drug Benefit Formulary.

^c The Ontario Drug Benefit Formulary price of ziprasidone has increased marginally since the manufacturer’s submission and has been updated in the cost comparison table. The marginal increase in price has not been reflected in this table, given that the direction of results is unchanged.

Table 5: Manufacturer’s Base-Case Results — Cost Comparison of Brexpiprazole Versus Other Oral SGA Comparators (Scenario 2)

Treatment	Range of Annual Cost (\$) ^a	Incremental Annual Cost (\$) ^b	
		Lower Recommended Dose	Upper Recommended Dose
Olanzapine (generic)	232.99 to 931.90	-1,045.38	-346.48
Olanzapine ODT (generic)	235.00 to 939.20	-1,043.37	-339.17
Quetiapine (generic)	253.96 to 507.92	-1,024.42	-770.46
Risperidone (generic)	443.56 to 665.34	-834.82	-613.04
Risperidone ODT (generic)	746.02 to 1,115.84	-532.35	-162.54
Quetiapine XR (generic)	765.56 to 1,531.13	-512.81	252.75
Brexpiprazole (Rexulti)	1,278.38	Reference	Reference
Ziprasidone (Zeldox) ^c	1,520.90	242.53	242.53
Lurasidone (Latuda)	1,570.58	292.20	292.20
Aripiprazole (Abilify)	1,571.20 to 1,854.26	292.82	575.89
Paliperidone ER (Invega)	2,034.77	756.07	756.07

ODT = oral disintegrating tablet; SGA = second-generation antipsychotic; XR = extended release.

^a Based on recommended doses. Costs do not include dispensing fees or markups.

^b Positive numbers indicate that the comparator costs more than brexpiprazole. All prices are from the Ontario Drug Benefit Formulary.

^c The Ontario Drug Benefit Formulary price of ziprasidone has increased marginally since the manufacturer’s submission and has been updated in the cost comparison table. The marginal increase in price has not been reflected in this table, given that the direction of results is unchanged.

The robustness of the manufacturer’s base-case results was tested through a variety of sensitivity analyses, including a “real-world” analysis using claims data from Ontario from the PharmaStat database (QuintilesIMS)¹⁰ to compare the weighted average daily cost of brexpiprazole to other oral SGAs when used in clinical practice. Results of this real-world sensitivity analysis were consistent with the primary analysis: the annual drug cost of brexpiprazole (\$1,278 per year), based on weighted average daily drug costs, was higher than that of standard generic and ODT olanzapine (\$452 and \$648 per year, respectively) and risperidone (\$191 and \$490 per year, respectively), as well as that of standard and extended-release quetiapine (\$119 and \$484 per year, respectively), but lower than the cost of branded comparators aripiprazole (\$1,617 per year), lurasidone (\$1,838 per year), paliperidone ER (\$2,252 per year), and ziprasidone (\$1,339 per year).

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