Common Drug Review
Pharmacoeconomic Review Report

November 2016

Drug	rotigotine (Neupro)
Indication	Treatment of the signs and symptoms of idiopathic Parkinson disease. Neupro may be used both as early therapy, without concomitant levodopa, and as an adjunct to levodopa.
Reimbursement request	List with similar criteria as pramipexole and ropinirole
Manufacturer	UCB Canada Inc.

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ABBREVIATIONS

APD	advanced Parkinson disease
CDR	Common Drug Review
DA	dopamine agonist
EPD	early Parkinson disease
NMA	network meta-analysis
ODB	Ontario Drug Benefit
PD	Parkinson disease

SUMMARY

Rotigotine (Neupro) is a transdermal delivery system (patch) available in the following strengths: 2 mg per 24 hours, 4 mg per 24 hours, 6 mg per 24 hours, and 8 mg per 24 hours. The manufacturer submitted the following prices: $3.54 (2 mg), $6.50 (4 mg), and $7.27 (6 mg and 8 mg) per patch, or $3.54 to $7.27 per day for the treatment of early Parkinson disease (EPD) and $6.50 to $14.54 per day for advanced Parkinson disease (APD). The manufacturer submitted a cost-minimization analysis, considering only drug costs, based on the assumption of similar efficacy among rotigotine, pramipexole, and ropinirole from the results of a network meta-analysis (NMA). The NMA showed that, for both EPD and APD, the efficacy of rotigotine, ropinirole, and pramipexole appeared similar at 11 to 16 weeks and 24 to 28 weeks after completion of the titration period. It is not clear if the findings of the NMA can be generalized to a longer time period, or to a population using different doses from those used in the clinical trials. Furthermore, the NMA did not assess the comparative safety profile of rotigotine with that of pramipexole and ropinirole.

At recommended doses, rotigotine (2 mg per 24 hours to 8 mg per 24 hours in EPD, and 4 mg per 24 hours to 16 mg per 24 hours in APD) is more expensive than generic pramipexole (1.5 mg to 4.5 mg daily, $0.79 to $2.37) and generic ropinirole (3 mg to 24 mg daily, $0.85 to $4.37), as well as other drugs used for the treatment of EPD and APD, such as oral levodopa-decarboxylase inhibitor combinations ($0.84 to $8.00 daily), entacapone ($0.40 to $3.21 daily), or monoamine oxidase B inhibitors ($1.00 to $7.00 daily). Consequently, the listing of rotigotine would result in additional costs.

The expected average maintenance doses of rotigotine used in the manufacturer's base-case scenario were likely underestimated, especially in APD. A Common Drug Review analysis showed that the price of rotigotine would need to be reduced by 51% to 88% to be equal to the average daily cost of generic pramipexole in EPD, and by 78% to 89% to be equal to the average daily cost of generic pramipexole in APD.

REVIEW OF THE PHARMACOECONOMIC SUBMISSION

1. INTRODUCTION

Rotigotine (Neupro), a non-ergolinic dopamine agonist (DA), is indicated for the treatment of the signs and symptoms of idiopathic Parkinson disease (PD). Rotigotine may be used both as early therapy, without concomitant levodopa, and as an adjunct to levodopa.[1] Rotigotine is a transdermal delivery system (patch) and is available in the following strengths: 2 mg per 24 hours ($3.54), 4 mg per 24 hours ($6.50), 6 mg per 24 hours ($7.27), and 8 mg per 24 hours ($7.27). At the submitted prices, the daily cost per patient is $3.54 to $7.27 for the treatment of early Parkinson disease (EPD), and $6.50 to $14.54 for advanced Parkinson disease (APD).[2]

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.

TABLE 1: COST COMPARISON TABLE FOR DRUGS IN EARLY AND ADVANCED IDIOPATHIC PARKINSON DISEASE

Drug / Comparator	Strength	Form	Price ($)	Recommended Daily Dose[a]	Daily Drug Cost ($)	Annual Cost ($)
Non-ergolinic DAs (Monotherapy in EPD or Combination with Levodopa/Decarboxylase Inhibitor in APD)						
Rotigotine (Neupro)	2 mg/24 hours 4 mg/24 hours 6 mg/24 hours 8 mg/24 hours	patch	3.5400[b] 6.5000[b] 7.2700[b] 7.2700[b]	EPD: 2 mg to 8 mg APD: 4 mg to 16 mg	3.54 to 7.27 6.50 to 14.54	1,292 to 2,654 2,372 to 5,307
Pramipexole (Generics)	0.25 mg 0.50 mg 1 mg 1.5 mg	tablet	0.2628 1.0514[e] 0.5257 0.5257	1.5 mg to 4.5 mg in 3 equal doses Average dose in EPD: 1.5 mg to 3 mg[f] Average dose in APD: 3 mg to 3.75 mg[f]	0.79[c] to 2.37[d] EPD: 0.79 to 2.37 APD: 1.58 to 2.37	284 to 865 EPD: 284 to 865 APD: 577 to 865
Ropinirole (Generics)	0.25 mg 1 mg 2 mg 5 mg	tablet	0.0710 0.2838 0.3122 0.8596	3 mg to 24 mg in 3 equal doses Average dose in EPD: 7 mg to 9 mg[f] Average dose in APD: 10 mg to 15 mg[f]	0.85 to 4.37 EPD: 1.15[g] to 79 APD: 2.11[h] to 2.58	310 to 1,595 EPD: 420 to 653 APD: 730 to 941

Drug / Comparator	Strength	Form	Price ($)	Recommended Daily Dose[a]	Daily Drug Cost ($)	Annual Cost ($)
Oral Levodopa/Decarboxylase Inhibitor Combinations (Monotherapy in EPD or Combination with Other Drugs in APD)						
Levodopa/ Carbidopa (Generics)	100 mg/10 mg 100 mg/25 mg 250 mg/25 mg	tablet	0.1877 0.2803 0.3129	300 mg to 1,500 mg of levodopa in 3 to 4 daily doses	0.84 to 1.88	307 to 686
	100 mg/25 mg 200 mg/50 mg	controlled release tablet	0.5126 1.0000	200 mg to 1,600 mg of levodopa in 2 to 4 daily doses	1.03 to 8.00	374 to 2,920
Levodopa/ Benserazide (Prolopa)	50 mg/12.5 mg 100 mg/25 mg 200 mg/50 mg	capsule capsule capsule	0.2830 0.4659 0.7821	400 mg to 800 mg of levodopa daily in 4 to 6 doses	1.86 to 3.73	679 to 1,361
COMT Inhibitors (in Combination with Levodopa/Decarboxylase Inhibitor in APD)						
Entacapone[i] (Generics)	200 mg	tablet	0.4010	200 mg to 1,600 mg daily in multiple doses	0.40 to 3.21	146 to 1171
Levodopa/ Carbidopa/ Entacapone (Stalevo)	50 mg/ 12.5 mg/200 mg 75 mg/ 18.75 mg/200 mg 100 mg/ 25 mg/200 mg 150 mg/ 37.5 mg/200 mg	tablet	1.6644	600 mg to 1,600 mg of entacapone daily in multiple doses	4.99 to 13.32	1,821 to 4,862
MAO-B Inhibitors (in Combination with Levodopa/Decarboxylase Inhibitor in APD)						
Rasagiline (Azilect)	0.5 mg 1 mg	tablet tablet	7.0000[j]	0.5 to 1 mg daily	7.00	2,555
Selegiline (Generics)	5 mg	tablet	0.5021	5 mg twice daily	1.00	367

APD = advanced Parkinson disease; COMT = catechol-O-methyltransferase; EPD = early Parkinson disease; MAO-B = monoamine oxidase B; ODB = Ontario Drug Benefit.
Source: Prices are from the ODB Formulary, November 2013, unless stated otherwise.
[a]Based on product monograph.
[b]Manufacturer-submitted price.
[c]The 0.5 mg tablet is not a benefit of the ODB Formulary. However, the 1 mg tablet is scored.
[d]The maximum daily cost is for a 2.25 mg dose (9 tablets of 0.25 mg daily) or a dose of 3.75 mg (1 mg + 0.25 mg three times daily).
[e]Saskatchewan Formulary, December 2013.
[f]Based on clinical expert's feedback, and mean doses from clinical trials.[3-8]
[g]Three doses of 2.25 mg.
[h]Three doses of 3.375 mg.
[i]Entacapone is indicated only as an adjunct to levodopa/carbidopa or levodopa/benserazide.
[j]ODB Exceptional Access Program (November 2013).

2. SUMMARY OF PHARMACOECONOMIC SUBMISSION

The manufacturer submitted two cost-minimization analyses:[2]

- The first analysis compared rotigotine with ropinirole and pramipexole as monotherapy for the treatment of EPD.
- The second analysis compared rotigotine as an adjunct to levodopa with ropinirole and pramipexole as an adjunct to levodopa for the treatment of APD.

For both EPD and APD, pramipexole and ropinirole were selected as the most appropriate comparators by the manufacturer, based on current treatment guidelines and clinical expert opinion.[2] The manufacturer noted that pramipexole should be considered the standard of care in both EPD and APD, based on Canadian utilization data provided in the manufacturer's submission, which showed that 79% of claims for DAs in Canada consisted of oral pramipexole (IMS Compuscript 2013).[2] The manufacturer assumed similar efficacy among rotigotine, pramipexole, and ropinirole, based on the results of two NMAs funded by the manufacturer: one for EPD (23 trials) and another one for APD (24 trials).[9] A summary and critical appraisal of the NMAs is presented in the Common Drug Review (CDR) clinical report (Appendix 8). The cost analysis was conducted from the public payer perspective over a one-year time horizon. Only drug costs associated with maintenance phase of treatment were included in the analyses and were obtained from the Ontario Drug Benefit (ODB) Formulary (2013). Other direct costs were assumed to be the same for all comparators.

For EPD, in the base-case analysis, based on internal forecast assumptions for the distribution of daily doses of rotigotine and the manufacturer's assumption of comparable dosages for pramipexole and ropinirole, the manufacturer estimated the weighted average daily maintenance doses to be 5.00 mg, 1.88 mg, and 7.50 mg, respectively. Based on these estimates, the manufacturer reported that rotigotine ($6.18 daily; $2,257 annually) was 373% ($1,652 annually) more expensive than pramipexole ($1.66 daily; $605 annually), and 442% ($1,746 annually) more expensive than ropinirole ($1.40 daily; $511 annually). The manufacturer performed a sensitivity analysis using the average daily dose at the end of maintenance phase from a non-systematic selection of clinical trials of the three comparators. It was not explained why only some of the trials used for the NMAs were included in the sensitivity analysis. The sensitivity analysis showed that rotigotine was 463% to 556% more expensive than pramipexole (incremental costs per year ranging from $2,353 to $3,236) and 306% to 390% more expensive than ropinirole (incremental costs per year ranging from $2,133 to $2,778).

Similarly for APD, the manufacturer estimated the weighted average daily maintenance doses to be 5.24 mg, 1.92 mg, and 7.86 mg, respectively. Based on these estimated doses, the manufacturer reported that rotigotine ($6.40 daily; $2,337 annually) was 386% ($1,732 annually) more expensive than pramipexole ($1.66 daily; $605 annually), and 434% ($1,798 annually) more expensive than ropinirole ($1.48 per day; $539 per year). The manufacturer performed a sensitivity analysis using the average daily dose at the end of maintenance phase from a non-systematic selection of clinical trials of the three comparators, and the sensitivity analysis showed that rotigotine was 692% to 715% more expensive than pramipexole (incremental costs per year ranging from $4,306 to $5,628) and 575% to 593% more expensive than ropinirole (incremental costs per year ranging from $4,158 to $5,439).

3. INTERPRETATIONS AND KEY LIMITATIONS

The following limitations with the manufacturer's analysis were noted:

- **Generalizability of the NMA results to a population using lower doses of rotigotine:** The manufacturer states that, according to a panel of Canadian physicians, the average daily dose of rotigotine observed in clinical trials would not reflect standard Canadian clinical practice.[2] As stated in the manufacturer's pharmacoeconomic submission, p. 21 and 23, *"the findings of the conducted MTC meta-analyses are generalizable to patients that share similar characteristics as those randomized in the included trials, and patients receiving similar doses of the considered interventions as those administered in the included trials."* Considering that the manufacturer expects the average maintenance daily dose of rotigotine to be lower than that observed in clinical trials for EPD and APD, it is unclear if the results of the NMAs can be generalized and if similar efficacy of rotigotine with pramipexole and ropinirole can be assumed. Furthermore, it is unknown if the safety profile of rotigotine is similar to that of pramipexole and ropinirole, since no safety outcomes were assessed in the NMAs.
- **Distribution of doses for rotigotine based on manufacturer's forecast assumptions instead of clinical trials:** There is an important difference between the average doses of rotigotine derived from the manufacturer's forecast and the mean doses observed at the end of the maintenance phase in clinical trials. The manufacturer expects the average maintenance daily dose of rotigotine to be 5 mg in EPD (compared with 5.7 mg to 8 mg in the clinical trials, which represents a 12% to 37.5% difference) and 5.24 mg in APD (compared with 10 mg to 13 mg in the clinical trials, which represents a 46% to 60% difference). No information was provided to the Canadian Agency for Drugs and Technologies in Health (CADTH) on the methodology or sources used to obtain the rotigotine dose distribution. In the absence of utilization studies, mean doses from clinical trials provide useful information on doses that might be used in actual practice. The estimated average maintenance dose of rotigotine was likely underestimated and the manufacturer's sensitivity analyses based on average doses from clinical trials might better reflect the potential incremental cost of rotigotine compared with pramipexole and ropinirole.
- **Underestimation of comparative dosage of rotigotine compared with pramipexole in APD:** The manufacturer assumed that the comparative dose ratio for rotigotine and pramipexole is 2.666:1. However, in study SP515 (Poewe et al.[3]), the authors noted that the failure to show non-inferiority of rotigotine versus pramipexole for the responder rates might indicate the need for a higher dose of rotigotine versus pramipexole than reflected by the 4:1 ratio reached in this trial.[3] Therefore, the estimated incremental cost of rotigotine compared with pramipexole in APD was likely underestimated (APPENDIX 1: COMMON DRUG REVIEW ANALYSIS FOR PRICE REDUCTION).
- **Lack of consideration of the progressive nature of PD:** It is unclear if the results of the NMAs, which were conducted for time intervals of 11 to 16 weeks and 24 to 28 weeks after completion of the titration period, can be generalized to one year. PD being a progressive condition, it is possible that the maintenance doses will increase over time, especially in advanced disease.

4. ISSUES FOR CONSIDERATION

- Utilization data from Ontario public plans showed that in July 2013 (latest data available at the time of the CDR review), 76% of claims for non-ergolinic DAs comprised pramipexole (Pharmastat data from IMS Health Canada Inc., 2013).
- A CDR analysis (APPENDIX 1: COMMON DRUG REVIEW ANALYSIS FOR PRICE REDUCTION) suggested that the price of rotigotine would need to be reduced by 51% to 88% to be equal to the average daily cost of generic pramipexole in EPD, and by 78% to 89% to be equal to the average daily cost of generic pramipexole in APD.

5. CONCLUSIONS

At recommended doses of rotigotine, the daily cost per patient ranges from $3.54 to $7.27 in EPD (2 mg per 24 hours to 8 mg per 24 hours), and $6.50 to $14.54 in APD (4 mg per 24 hours to 16 mg per 24 hours). Rotigotine is more expensive than generic pramipexole ($0.79 to $2.37 per patient per day) and generic ropinirole ($0.85 to $4.37 per patient per day), as well as other drugs used for the treatment of early or APD, such as oral levodopa-decarboxylase inhibitor combinations ($0.84 to $8.00 per patient per day), entacapone ($0.40 to $3.21 per patient per day), or MAO-B inhibitors ($1.00 to $7.00 per patient per day). Consequently, the listing of rotigotine would result in additional costs.

The expected average maintenance doses of rotigotine used in the manufacturer's base-case scenario were likely underestimated, especially in APD. A CDR analysis showed that the price of rotigotine would need to be reduced by 51% to 88% to be equal to the average daily cost of generic pramipexole in EPD, and by 78% to 89% to be equal to the average daily cost of generic pramipexole in APD.

APPENDIX 1: COMMON DRUG REVIEW ANALYSIS FOR PRICE REDUCTION SCENARIOS

A CDR analysis of utilization data from Ontario public plans showed that in July 2013 (latest data available at the time of the CDR review), 76% of claims for non-ergolinic DAs comprised pramipexole (Pharmastat data from IMS Health Canada Inc., 2013).

The manufacturer applied a 2.666:1 ratio between rotigotine and pramipexole doses, for both EPD and APD, based on the 2013 Human Drug Advisory Panel New Medicine Review report by the Patented Medicine Prices Review Board.[2]

In EPD, there are no randomized controlled trials that directly compare rotigotine to pramipexole. The clinical expert consulted for this review, as well as clinical trials in EPD,[8] suggested that the average daily maintenance dose of pramipexole in EPD ranges between 1.5 mg and 3 mg. Applying the 2.666:1 ratio submitted by the manufacturer, CDR calculated the cost reduction that would be required to produce an average daily cost of rotigotine that would be equivalent to the average daily cost of generic pramipexole in EPD. As shown in Table 2, the price of rotigotine would need to be reduced by 51% to 88% to be equal to the average daily cost of generic pramipexole in EPD.

In APD, one double-blind randomized controlled trial directly compared rotigotine with pramipexole (SP515, Poewe et al.[3]). Rotigotine was non-inferior to pramipexole for the change in off time, but responder rates (proportion of patients with ≤ 30% reduction in absolute off time per day) were greater in the pramipexole group, and rotigotine was not shown to be non-inferior to pramipexole for this end point.[3] Mean doses at the start of the maintenance phase were 12.95 mg for rotigotine and 3.1 mg for pramipexole. As noted by the authors in the discussion section, *"This finding, as well as the numerical differences in absolute off time reduction in favour of pramipexole, might indicate a somewhat higher equivalence dose for rotigotine versus pramipexole than reflected by the 4 to 1 ratio reached in this trial."*[3]

The clinical expert consulted for this review, as well as clinical trials in APD,[3,5] suggested that the average daily maintenance dose of pramipexole in APD ranges between 3 mg and 4 mg. CDR calculated the cost reduction that would be required to produce an average daily cost of rotigotine equivalent to the average daily cost of generic pramipexole in APD. Two equivalence ratios were assessed to compare rotigotine to pramipexole: 2.666:1 (as submitted by the manufacturer), and 4:1 (as observed in SP515). As shown in Table 2, the price of rotigotine would need to be reduced by 78% to 89% to be equal to the average daily cost of generic pramipexole in APD.

TABLE 2: COMMON DRUG REVIEW ANALYSIS FOR PRICE REDUCTION SCENARIOS FOR ROTIGOTINE

Average Daily Dose of Pramipexole	Daily Cost of Pramipexole (Generics) ($)	Equivalent Daily Dose of Rotigotine	Daily Cost of Rotigotine[a] ($)	% Rotigotine Price Reduction Needed to Equal the Daily Cost of Pramipexole ($ price)
EPD				
Manufacturer's Base-Case Scenario Weighted dosing approach and 2.666:1 equivalence ratio between rotigotine and pramipexole doses				
1.88 mg	1.6600	5.00 mg	6.18	73% ($1.66)
CDR Analysis Average doses of pramipexole from clinical trials and clinical expert input, assuming a 2.666:1 equivalence ratio between rotigotine and pramipexole doses				
1.5 mg[b] (0.25 mg x 2 x 3) (0.5 mg x 3) (1 mg x 1.5)	 1.5768 3.1542 0.7886	4 mg	6.50	 76% ($1.56) 51% ($3.18) 88% ($0.78)
3 mg (3 x 1 mg)	1.5771	8 mg	7.27	78% ($1.60)
APD				
Manufacturer's Base-Case Scenario Weighted dosing approach and 2.666:1 equivalence ratio between rotigotine and pramipexole doses				
1.92 mg	1.6600	5.24 mg	6.40	74% ($1.66)
CDR Analysis Average doses of pramipexole from clinical trials and clinical expert input, assuming a 2.666:1 equivalence ratio between rotigotine and pramipexole doses				
3 mg (3 x 1 mg)	1.5771	8 mg	7.27	78% ($1.60)
3.75 mg (3 x 1.25 mg)	2.3655	10 mg (4 mg + 6 mg)	13.77	83% ($2.34)
CDR Analysis Average doses of pramipexole from clinical trials and clinical expert input, assuming a 4:1 equivalence ratio between rotigotine and pramipexole doses				
3 mg (3 x 1 mg)	1.5771	12 mg (2 x 6 mg)	14.54	89% ($1.60)
3.75 mg (3 x 1.25 mg)	2.3655	16 mg (2 x 8 mg)	14.54	84% ($2.33)

CDR = Common Drug Review; ODB = Ontario Drug Benefit.
Note: Pramipexole price (generics) is from the ODB Formulary, November 2013, except for the 0.5 mg tablet (Saskatchewan online formulary database, December 2013, $1.0514 per 0.5 mg tablet).
[a]Manufacturer-submitted price.
[b]The 0.5 mg is not a benefit on the ODB Formulary. However, it is available in some provinces, such as Saskatchewan, Manitoba, and New Brunswick. The 1 mg tablet is scored and, therefore, 1.5 tablets of 1 mg per day (1/2 tablet x 3) could be used.

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